Review

Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

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Abstract

Background: Primary multiple simultaneous intracerebral hemorrhages (MSICHs) are quite rare. Although occasional reports have been found, there have been no systematic reviews. The published case reports and case series contain overlapping data, leading to erroneous information about MSICHs. This is the first extensive review of accessible studies published in English on MSICHs. Our primary objective was to analyze the demographic data on age, sex, outcome and prognosis with regard to primary MSICHs. ***Summary:*** A PubMed search without language restriction for articles with results from human studies and registered between January 1950 and September 2013 yielded 677 articles. The following inclusion criteria were applied: (1) reported case(s) or case series on primary MSICHs; (2) text partly or fully in English, and (3) text contains identifiable data on age, sex and outcome of patients. A total of 24 articles met all the inclusion criteria. The reference lists of these 24 articles were inspected for additional relevant articles, which yielded another 20 articles. In all, 248 cases were identified; 143 cases were excluded for various reasons: 52 duplicate cases, 18 cases of multiple nonsimultaneous intracerebral hemorrhages, 25 cases of secondary MSICHs, and 48 cases with incomplete data on age, sex and outcome. The remaining 105 cases were analyzed. MSICHs were found to be more common in bilateral cases (53.33%): there were bilateral basal ganglia hemorrhages (33.33%), bilateral thalamic hemorrhages (18.10%), bilateral lobar hemorrhages (0.95%) and bilateral cerebellar hemorrhages (0.95%). Nonbilateral MSICHs were found in 46.67% of the cases. The hematomas were commonly distributed in the basal ganglia (45.83%), thalamus (30.56%) and cerebellum (10.19%). MSICHs were more frequently encountered in males (60.95%; average age: 59.13 ± 12.49 years). The average age of the female patients was

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KARGER

103

Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

higher (63.89 ± 13.11 years). Patients with primary MSICHs had a survival rate of 56.20%. There was a favorable outcome of primary MSICHs in 18.10% of all the cases, the highest proportion of which was in the nonbilateral MSICH group. The remaining 38.10% had unfavorable outcomes. Death occurred in 43.80% of all cases, the highest proportion being found in the bilateral basal ganglia hemorrhage group. Primary MSICHs share features with solitary intracerebral hemorrhage regarding age, sex, and the location and distribution of hematomas, but they have a poorer outcome (p < 0.05). **Key Messages:** Primary MSICHs are rare and share features with solitary intracerebral hemorrhage regarding age and the location and distribution of hematomas. Patients have a poorer prognosis but higher favorable outcome rates in case of survival. This information adds to the awareness of clinicians that higher rates of favorable outcomes can be achieved for MSICHs.

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Introduction

Intracerebral hemorrhage is an important clinical condition leading to severe disability and a high mortality rate. A rare type of stroke, even in the era of CT scanning, is that of multiple simultaneous intracerebral hemorrhages (MSICHs) [1]. Primary MSICHs are defined as two discrete primary intracerebral hemorrhages occurring simultaneously or within 24 h since the first identified intracerebral hemorrhage [1].

Ten to twenty percent of all strokes are spontaneous intracerebral hemorrhages [2, 3]. The incidence of MSICHs is up to 5.6% of all spontaneous intracerebral hemorrhages. However, MSICHs occur more commonly in a secondary form [1], and primary MSICHs have a much lower incidence varying from 0.75 to 3.0% of all cases of spontaneous intracerebral hemorrhage [1, 4]. The overall outcome and prognosis are also poorer than with primary solitary intracerebral hemorrhages [1, 4].

Although primary MSICHs are a rare condition, sporadic case reports, case series and summaries of cases have continuously been published worldwide. In the details of these reports, cross-references, data duplication, missing data, and cases of secondary MSICHs and nonsimultaneous multiple intracerebral hemorrhages are to be found. Nevertheless, data on true primary MSICHs can be extracted from them. A pooled data analysis will show the benefit of having more accurate clinical features of MSICHs. Still, one major obstacle is constituted by the different objectives of the published articles, precluding the assessment of some of the case data.

Currently, there is no systematic review of primary MSICHs. Therefore, the present review sheds some light on this rare condition. We provide an outline for epidemiologic features of MSICHs as well as for clinical outcome. The present study aimed to review MSICHs systematically, to clarify the data on and analyze published cases of primary MSICHs since 1954 [5], and to analyze the location and distribution of hematomas as well as the age, sex and outcomes of patients with MSICHs.

Materials and Methods

The present review was prepared systematically in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We conducted a PubMed search for articles with results from human studies, with no language restriction, that were registered between January 1950 and September 2013. The search yielded 677 articles.

Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

These 677 articles were screened for their title, abstract and keywords, identifying the relevance of their treatment of MSICHs and excluding duplicates and irrelevant articles. The included articles were case reports and case series on primary MSICHs, with part of the text or the full text in English and with identifiable data on the age, sex and outcome of patients. The aforementioned process yielded 24 articles which met the inclusion criteria. The reference lists of these 24 selected articles were inspected as well, yielding an additional 20 articles. In all, 44 articles – 27 full texts and 17 abstracts – were selected for our review. The remaining 653 articles were excluded.

Case Eligibility

There were 248 identifiable cases of MSICHs assessed in these 44 articles; 52 duplicates were identified and excluded. Another 91 cases were excluded for various reasons: 18 cases with multiple nonsimultaneous intracerebral hemorrhages, 25 cases with secondary MSICHs, and 48 cases with incomplete data on age, sex and outcome. The remaining 105 cases of primary MSICHs with complete data on age, sex and outcome were studied and analyzed in detail.

Results

Epidemiologic Features and Location of the Hematomas

A total of 35 articles (table 1) are from Asian countries: 26 articles are from East Asia, with 17 from Japan [4, 8–10, 13, 14, 16, 17, 30, 34, 36–39, 41, 42, 46], 6 from Korea [11, 12, 15, 18, 24, 40] and 3 from Taiwan [19, 32, 35], and 9 articles are from other Asian countries, with 3 from India [20, 23, 29], 3 from Turkey [22, 25, 26], 2 from Iraq [28, 31] and 1 from Nepal [27]. The remaining 9 articles are from outside Asia: 1 from Serbia in Europe [21], 6 from the USA [1, 5–7, 43, 44], and 1 each from Cuba in the Caribbean [45] and Argentina in South America [33].

In the 105 selected cases, there were 216 hematomas distributed in both the supratentorial and the infratentorial regions. The supratentorial region was the location of 181 hematomas (83.80%), distributed between the following brain areas: the lobar region (16 hematomas; 7.41%), basal ganglia (99 hematomas; 45.83%) and thalamus (66 hematomas; 30.56%). The hematomas were found to be nearly equally distributed between the left and the right hemisphere, with 91 and 90 hematomas, respectively (fig. 1). The infratentorial region contained fewer hematomas (n = 35; 16.20%): 2 (0.92%) in the midbrain, 11 (5.09%) in the pons and 22 (10.19%) in the cerebellum, as shown in figure 1.
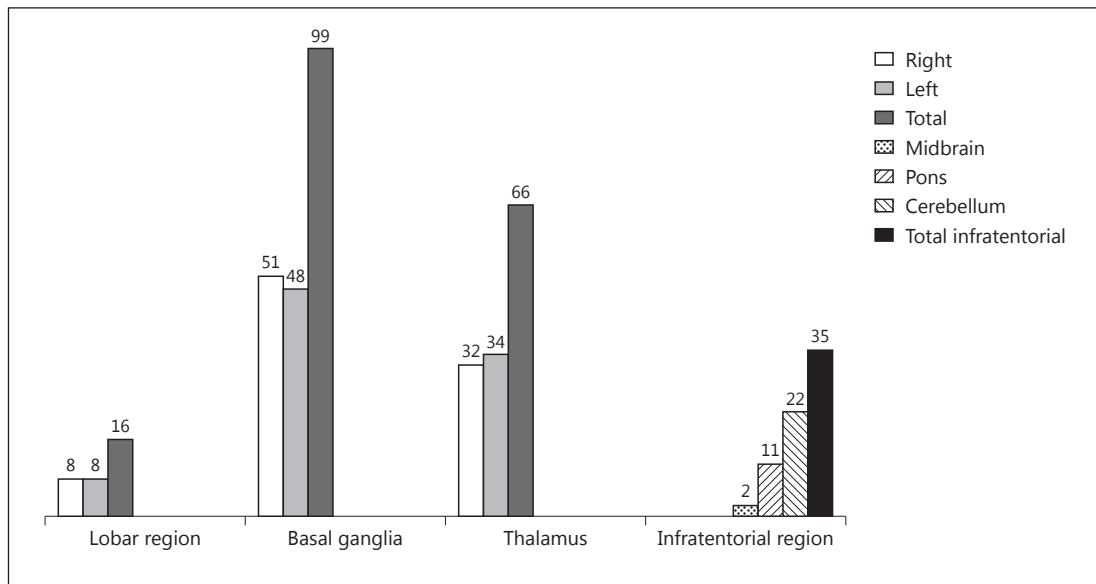
The primary MSICHs could also be categorized into bilaterally located (56 cases; 112 hematomas) and nonbilaterally located hematomas (49 cases; 104 hematomas). Bilateral MSICHs were found in certain brain regions, i.e. the lobar region, basal ganglia, thalamus and cerebellum. Bilateral lobar hemorrhages were found in 1 case (0.95%), in the bilateral occipital lobes, as reported in 1997 [13]. The most common area of bilateral MSICHs was the bilateral basal ganglia (table 2) with 35 cases (33.33%); this was followed by bilateral thalamic hemorrhages, which were found in 19 cases (18.10%). The cerebellum was the most common location of hematomas in the infratentorial region, but bilateral cerebellar hemorrhages were found in only 1 case (0.95%), as reported recently in 2012 (table 2) [29].

Another category of MSICHs is the nonbilateral one. In the 49 cases of nonbilateral MSICHs, 6 cases had 3 hematomas and 43 cases had 2 hematomas (table 3). The total number of hematomas was 104 (table 3). They were found to be distributed between the following brain areas: the lobar region (14 hematomas), basal ganglia (29 hematomas), thalamus (28 hematomas), midbrain (2 hematomas), pons (11 hematomas) and cerebellum (20 hema-
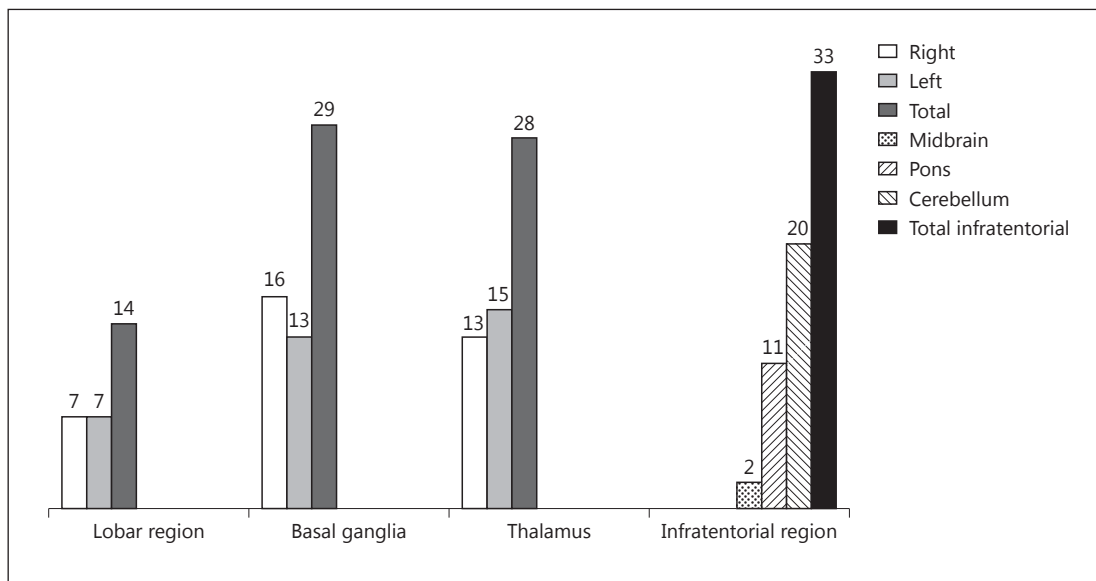
Table 1. Summary of the literature (case reports, case series and case summaries)

Authors	Year	Cases			Type of text	Searching method
		Identifiable	Eligible	Ineligible		
Case reports						
Hartson [5]	1954	1		1[a]	title	electronic search
Tucker et al. [6]	1980	2		2[a]	abstract	electronic search
Hickey et al. [7]	1983	2	2 (from Ohta and Yokota [42])		abstract	electronic search
Tanikake et al. [8]	1983	2	1 (from Ohta and Yokota [42])	1[a]	abstract	electronic search
Sato et al. [9]	1986	3	1	1[a]; 1[b]	full text	hand search
Kabuto et al. [10]	1995	2	2		full text	electronic search
Kim et al. [11]	1995	1	1		abstract	hand search
Joo et al. [12]	1997	2	2		abstract	hand search
Nakamura et al. [13]	1997	1	1		abstract	electronic search
Sunada et al. [14]	1999	1	1		abstract	electronic search
Lee et al. [15]	1999	1	1		abstract	hand search
Kohshi et al. [16]	2000	2	2		full text	electronic search
Kazui et al. [17]	2001	1		1[c]	full text	hand search
Choi et al. [18]	2005	1	1		full text	hand search
Hsieh et al. [19]	2006	1	1		full text	hand search
Asimi et al. [20]	2007	1	1		abstract	hand search
Kuljic-Obradovic et al. [21]	2007	1		1[d]	full text	electronic search
Ozdemir et al. [22]	2007	1	1		full text	electronic search
Balasubramaniam et al. [23]	2007	1	1		full text	electronic search
Kim and Cho [24]	2008	1	1		full text	hand search
Terzi et al. [25]	2010	1	1		full text	electronic search
Akar and Bayrak [26]	2010	1	1		full text	hand search
Lamichhane and Paudel [27]	2010	1	1		full text	hand search
Amin et al. [28]	2010	1	1		full text	hand search
Lalla et al. [29]	2012	1	1		full text	hand search
Ohba et al. [30]	2012	1	1		abstract	hand search
Amin [31]	2013	1	1		abstract	electronic search
Case series						
Lin et al. [32]	1993	6	1 (from Perez et al. [45]); 2 (from Silliman et al. [43])	3[a]	abstract	electronic search
Mauriño et al. [33]	2001	4	4		full text	electronic search
Shiomi et al. [34]	2004	11		11[a]	abstract	hand search
Yen et al. [35]	2005	10	10		full text	electronic search
Sorimachi et al. [36]	2007	9		9[a]	full text	electronic search
Stemer et al. [1]	2010	29		15[d]; 14[a]	full text	electronic search
Takeuchi et al. [37]	2011	20	20		full text	electronic search
Case summaries						
Miyasaka et al. [38]	1982	20	2	16[c]; 2[a]	full text	hand search
Tanno et al. [4]	1989	5	5		abstract	hand search
Uno et al. [39]	1991	9	8	1[a] (from Ohta and Yokota [42])	abstract	hand search
Bae et al. [40]	1997	3		3[a]	abstract	hand search
Imai [41]	2000	10	6	4[d]	full text	electronic search
Ohta and Yokota [42]	2003	21	2	19[b]	full text	hand search
Silliman et al. [43]	2003	7	1	6[b]	full text	electronic search
Finelli [44]	2006	3	1	2[d]	full text	electronic search
Perez et al. [45]	2009	18	1	1[c]; 1[d]; 15[b]	full text	electronic search
Masayoshi et al. [46]	2010	28	15	11[b]; 2[d]	full text	hand search

[a] Incomplete data. [b] Duplicate case. [c] Nonsimultaneous. [d] Not primary hemorrhages.

Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

Fig. 1. Hematoma distribution (216 hematomas in 105 cases).

Fig. 2. Hematoma distribution of nonbilateral MSICHs (104 hematomas in 49 cases).

tomas). Although the name 'nonbilateral MSICHs' misleadingly suggests an uneven distribution of hematomas between the left and the right side of the brain, they were found to be nearly equally distributed, with 36 hematomas in the right hemisphere and 35 hematomas in the left (fig. 2).

The nonbilateral MSICHs were further categorized by hematoma location into those exclusively located in the supratentorial region, those exclusively located in the infratentorial region and those located in the combined supra-infratentorial region. The majority of the

Table 2. Location of hematomas

	Cases, n (%)	Hematomas, n (%)
Bilateral lobar hemorrhages	1 (0.95)	2 (0.93)
Bilateral basal ganglia hemorrhages	35 (33.33)	70 (32.40)
Bilateral thalamic hemorrhages	19 (18.10)	38 (17.59)
Bilateral cerebellar hemorrhages	1 (0.95)	2 (0.93)
Nonbilateral MSICHs	49 (46.67)	104 (48.15)
Total	105 (100)	216 (100)

Table 3. Nonbilateral MSICHs

	Cases, n (%)	Hematomas, n (%)
Total	49 (100)	104 (100)
Exclusively in supratentorial region	19 (38.78)	41 (39.42)
3 hematomas per case	3	9
2 hematomas per case		
Basal ganglia and thalamus	10	20
Lobar region and thalamus	3	6
Lobar region and basal ganglia	1	2
Lobar region only	1	2
Ipsilateral caudate and putamen	1	2
Exclusively in infratentorial region	2 (4.08)	4 (3.85)
Pons and cerebellum	2	4
Combined supra-infratentorial region	28 (57.14)	59 (56.73)
3 hematomas per case	3	9
2 hematomas per case		
Thalamus and cerebellum	9	18
Basal ganglia and pons	6	12
Basal ganglia and cerebellum	6	12
Lobar region and cerebellum	2	4
Basal ganglia and midbrain	1	2
Thalamus and pons	1	2

nonbilateral MSICHs were in the combined supra-infratentorial region (28 cases; table 3); the combination of thalamus and cerebellum was the most common (9 cases). The combinations of basal ganglia and pons and of basal ganglia and cerebellum followed with 6 cases each. Other combinations included the lobar region and cerebellum (2 cases), the basal ganglia and midbrain (1 case), and the thalamus and pons (1 case). The remaining 3 cases had 3 hematomas each.

There were 19 cases of nonbilateral MSICHs exclusively in the supratentorial region. The most common combination there was that of basal ganglia and thalamus (10 cases). This was followed by the combination of the lobar region and thalamus (3 cases): 1 case each had hematomas in the lobar region and basal ganglia, in the lobar region only, and in the ipsilateral caudate and putamen. There were 3 cases with 3 hematomas each (table 3). There were 2 cases with hematomas found exclusively in the infratentorial region. Both had hematomas simultaneously in the pons and cerebellum (table 3).

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Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

Table 4. Age range and average age of patients with MSICHs

	Cases, n	Age range, years	Average age ± SD, years
Total	105	28–94	60.98±12.88
Males	64	28–89	59.13±12.49
Females	41	33–94	63.89±13.11
Bilateral lobar hemorrhages	1		
Males	1	55	55
Bilateral basal ganglia hemorrhages	35	35–89	59.66±12.90
Males	22	35–89	59.95±12.87
Females	13	40–89	59.15±13.45
Bilateral thalamic hemorrhages	19	28–82	64.58±12.92
Males	13	28–80	59.92±12.68
Females	6	68–82	74.67±6.02
Bilateral cerebellar hemorrhages	1		
Males	1	38	38
Nonbilateral MSICHs	49	29–94	61.12±12.69
Males	27	29–80	59.00±12.29
Females	22	33–94	63.73±12.96

Age and Sex Distribution

MSICHs were found to be more common in male patients (60.95%). The male-to-female ratio was 1.56:1 (64:41; table 4). The 105 selected cases had an average age of 60.98 ± 12.88 years (range: 28–94 years). The males had a lower average age than the females: the average age of the male patients was 59.13 ± 12.49 years (range: 28–89 years), whereas that of the female patients was 63.89 ± 13.11 years (range: 33–94 years; table 4).

Bilateral lobar hemorrhages and bilateral cerebellar hemorrhages were encountered in 1 male patient each, aged 55 and 38 years, respectively. Bilateral basal ganglia hemorrhages were encountered in 22 males with ages ranging from 35 to 89 years and an average age of 59.95 ± 12.87 years, and in 13 females with ages ranging from 40 to 89 years and an average age of 59.15 ± 13.45 years (table 4). There were 19 cases of bilateral thalamic hemorrhages: 13 were males with ages ranging from 28 to 80 years and an average age of 59.92 ± 12.68 years, and 6 were females with ages ranging from 68 to 82 years and an average age of 74.67 ± 6.02 years (table 4). The 49 cases of nonbilateral MSICHs included 27 males with ages ranging from 29 to 80 years and an average age of 59.00 ± 12.29 years and 22 females with ages ranging from 33 to 94 years and an average age of 63.73 ± 12.96 years (table 4).

Outcome

Although the outcome and prognosis of primary MSICHs are mentioned in the literature, i.e. a poor outcome and grave prognosis [4], they are not described in detail for this category. The present study shows the mortality rate to be 43.80% (46 of 105 cases) and the survival rate to be 56.20% (59 of 105 cases). The majority of the surviving patients (40; 38.10%) had unfavorable outcomes, whereas the remaining 19 patients (18.10%) had favorable outcomes. This reflects the high mortality rate and poor prognosis associated with MSICHs (table 5).

Both bilateral lobar hemorrhages and bilateral cerebellar hemorrhages had favorable outcomes. Bilateral basal ganglia hemorrhages had the highest mortality rate (60%; 21 of 35 cases) and the worst prognosis. Approximately one third (34.29%; 12 of 35 cases) had unfavorable outcomes; only 5.71% (2 of 35 cases) had favorable outcomes. The mortality rate for bilateral thalamic hemorrhages was 31.58% (6 of 19 cases). The survival rate was 69.42%

Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

Table 5. Outcome of MSICHs

	Cases, n	Survival, n		Death, n
		favorable	unfavorable	
Bilateral lobar hemorrhages	1	1	0	0
Bilateral basal ganglia hemorrhages	35	2	12	21
Bilateral thalamic hemorrhages	19	4	9	6
Bilateral cerebellar hemorrhages	1	1	0	0
Nonbilateral MSICHs	49	11	19	19
Total	105	19 (18.10%)	40 (38.10%)	46 (43.80%)

Table 6. Relation of primary outcome and mortality to location of MSICHs (χ^2 test)

	Cases, n	Outcome	Mortality
Bilateral lobar hemorrhages	1	0.033*	0.102
Bilateral basal ganglia hemorrhages	35	0.020*	0.018*
Bilateral thalamic hemorrhages	19	0.398	0.27
Bilateral cerebellar hemorrhages	1	0.033*	0.102
Nonbilateral MSICHs	49	0.278	0.331
Total	105	0.000*	0.205

* p < 0.05.

(13 of 19 cases); of these 19 cases, 4 (21.05%) had favorable outcomes, while 9 (47.37%) had unfavorable outcomes. The mortality rate for nonbilateral MSICHs was 38.78% (19 of 49 cases); the remaining 30 patients (61.22%) survived, of whom 19 (38.78%) had unfavorable outcomes and 11 (22.44%) had favorable outcomes.

Although the mortality rates were high, no statistical significance was found in the relationship between mortality rate and total MSICHs (p > 0.05). In contrast, prognosis showed a strong statistical significance regarding total MSICHs and poorer outcome (p < 0.05). Bilateral basal ganglia hemorrhages were statistically significantly related to both poorer outcome and mortality (p < 0.05; table 6). On the other hand, both bilateral lobar and bilateral cerebellar hemorrhages were statistically significantly related to outcome, which was favorable in both cases, even though there was only 1 case per group. Bilateral thalamic hemorrhages and nonbilateral MSICHs were not statistically significantly associated with either mortality or prognosis.

Discussion

Epidemiologic Features

Stroke is a devastating condition with high rates of mortality and morbidity, ranking fourth among all causes of death, following heart diseases, cancer and chronic lower respiratory diseases [2]. The overall prevalence of stroke is approximately 3% in the general population [2]. Spontaneous intracerebral hemorrhages constitute 10–20% of all strokes [2, 3].

Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

Primary intracerebral hemorrhages account for 75% of intracerebral hemorrhages. Primary intracerebral hemorrhages are intracerebral hemorrhages without an identifiable structural cause of the hemorrhage or acute insult to the vascular or coagulation system. Primary solitary intracerebral hemorrhages are more common in male patients, particularly those who are older than 55 years. People of Asian descent have a higher incidence of primary intracerebral hemorrhage [47].

MSICHs occur in 5.6% of spontaneous intracerebral hemorrhages [1]. A few studies have found the incidence of primary MSICHs to vary from 0.7–1.08% [4, 32, 46] to 2–3.4% [1, 33] of primary intracerebral hemorrhages. Primary MSICHs have a much lower incidence than secondary MSICHs (3.4 and 13.6%, respectively) [1]. The present study shows the prevalence of MSICHs in Asia, particularly in East Asia, Japan, Korea and Taiwan. According to our findings, 26 of 44 reports came from East Asia. This indirectly indicates a high incidence of MSICHs in Asian countries together with the incidence of primary intracerebral hemorrhages.

The first report of primary MSICHs was made on 1 case in the *Bulletin of the Los Angeles Neurological Society* in 1954 [5]. Unfortunately, only the title of this article could be accessed, and there was no additional information on the case. The earliest case of primary MSICHs with complete data was identified in 1977 [46]; in this case, the hemorrhages were found in the bilateral basal ganglia. Bilateral thalamic hemorrhages were first reported later, in 1981 [45]. There was only 1 case of bilateral lobar hemorrhages, which were found in the bilateral occipital lobes; this case was reported in 1997 [13]. The only case of bilateral cerebellar hemorrhages was recently reported in 2012 [29]. Nonbilateral primary MSICHs were first reported in 1982; they were a combination of basal ganglia and thalamic hemorrhages [38].

Age and Sex Distribution

Primary solitary intracerebral hemorrhages are more common in male patients and slightly younger female patients [35, 48]. The present study shows an average age of 60.98 years for the 105 selected patients with primary MSICHs. MSICHs were more common in the male patients (64 cases; 60.95%). The male-to-female ratio was 1.56:1. The female patients were found to be older than the male patients, with an average age of 63.89 versus 59.13 years. The age and sex distribution of primary MSICHs was found to be no different from that of primary solitary intracerebral hemorrhages.

Location of Hematomas

Primary solitary intracerebral hemorrhages commonly occur in the lobar region, basal ganglia, thalamus, brain stem and cerebellum [49]. Primary MSICHs have the same hematoma locations as primary solitary intracerebral hemorrhages [35, 46]. For MSICHs, the present study shows that the hematomas were most commonly located in the basal ganglia (45.83%), followed by the thalamus (30.56 %), cerebellum (10.19%), lobar region (7.41%) and brain stem (6.31%), including the midbrain and the pons.

Bilateral primary MSICHs were most commonly found in the basal ganglia (33.33%). Bilateral thalamic hemorrhages were also commonly found (18.1%), while bilateral lobar and cerebellar hemorrhages were least commonly encountered and have been identified in only 1 case each (0.95%).

Nonbilateral primary MSICHs were encountered in 46.67% of the cases. The combinations of hematoma locations are ranked from most to least common, as follows: basal ganglia and thalamus (10 cases), thalamus and cerebellum (9 cases), basal ganglia and pons (6 cases), and basal ganglia and cerebellum (6 cases). Although the name 'nonbilateral primary MSICHs' suggests an unequal distribution of hematomas, these hematomas were found to be distributed in nearly equal numbers between the right and the left side of the individual locations. These

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111

Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between
1950 and 2013: Analysis of Data on Age, Sex and Outcome

findings confirm the conclusion that there is no preponderance of one side over the other for hematomas in nonbilateral primary MSICHs.

Pathophysiologic Features

The two main causes of primary intracerebral hemorrhage are hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) [3, 50]. Arterial hypertension was present in 75.6% of patients with spontaneous intracerebral hemorrhage and was proven to be a risk factor for it [2, 51, 52]. Nearly all the articles on primary MSICHs found the condition to be associated with hypertension. There were 2 articles that reported evidence for CAA in MSICHs: a study from 1980 reported 2 cases, but they were excluded from the study due to incomplete data on age, sex and outcome [6]; the other study found indirect evidence for amyloid angiopathy, i.e. a low cystatin C concentration in the cerebrospinal fluid [13]. Therefore, hypertension is one of the main diseases associated with primary MSICHs.

Hypertension and CAA have widespread effects on the cerebral vasculature and autoregulation mechanism. Chronic and long-standing hypertension causes hyperplastic arteriolosclerosis, leading to fragile vessels [35]. In CAA, β-amyloid protein deposition in the cerebral arteriolar smooth muscles causes a degeneration of the vessel wall, which leads to pressure-passive cerebral circulation and fragile vessels [53]. A detailed discussion of hypertensive vasculopathy and CAA is beyond the scope of this study but can be found elsewhere [53].

A few hypotheses have been made on possible mechanisms in the context of a widespread fragile cerebral vasculature and impaired autoregulation mechanism. In 1995, a first mechanism was proposed for the incidental simultaneous rupture of fragile vessels [4, 35]. A second possible mechanism was proposed a decade later in 2005, suggesting that the initial hemorrhage causes a reflex increase in blood pressure and intracranial pressure, resulting in bleeding in other brain areas [18]. A third possible mechanism was proposed in 2011 and was similar to the second mechanism. With the hemorrhage-induced pain and coinciding release of catecholamines, hypertension worsens, thereby causing additional hemorrhage in diseased vessels [54]. In the end, the exact pathophysiology of primary MSICHs remains unclear.

Outcome and Prognosis

The prognosis of primary MSICHs was previously believed to be grave and worse than that of primary solitary intracerebral hemorrhage [35]. The mortality rate of patients with hemorrhagic stroke is reported to be very high at 37–44% and to vary with age [2, 55, 56], which is comparable with our study, in which the overall death rate of patients with MSICHs was 43.80%.

The occurrence of good functional outcomes is substantially reduced with primary intracerebral hemorrhage; only a small percentage of patients (11–12%) achieves good functional outcomes [2, 57, 58]. The present study, however, shows the percentage of favorable outcomes to be as high as 18.10% for primary MSICHs. More intensive care might be required for patients with MSICHs to provide them with a better chance of having favorable outcomes.

However, there were some differences in prognosis and outcome between the subtypes of MSICHs; patients with bilateral basal ganglia hemorrhages, for instance, had the worst prognosis, the highest mortality rate (60%) and the lowest percentage or favorable outcomes (5.71%). These findings have statistical significance. Unfavorable outcomes were found to be most frequent in patients with bilateral thalamic hemorrhages (47.37%), but there was no statistical significance.

Secondary MSICHs

To complete the present review, secondary MSICHs will be briefly discussed. Secondary MSICHs were found to be the most common type of simultaneous intracerebral hemorrhages,

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112

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Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between
1950 and 2013: Analysis of Data on Age, Sex and Outcome

accounting for up to 13.6% of MSICHs [1]. Multiple etiologies have been suggested for secondary MSICHs. The most common cause is hematologic abnormalities [1]. Other etiologies include concomitant anticoagulant use, novel antithrombotic drug treatment, venous sinus thrombosis, vasculitis, cerebral metastasis and cardiopulmonary resuscitation [35, 59–61].

Study Limitation and Future Direction

The major limitation to the present study is the rarity of the condition under investigation, leading to unpublished or underdiagnosed cases. Although an exact account of its history, outcome and prognosis may not be completely achieved, the present paper has given an outline from the available published data.

An interesting topic is that MSICHs contain multiple hematomas inside the brain. These multiple simultaneous lesions in the brain may produce a different intracranial pressure in the area containing the hematomas, which may affect treatment options and outcomes. According to our study, favorable outcome rates are higher for MSICHs than for solitary intracerebral hemorrhages. From a modern neurologic perspective, neurologic intensive care and multimodal treatment may yield great benefit to patients with MSICHs, improving prognosis and outcome. A thorough study of the treatment options for and outcomes of MSICHs would provide optimal solutions with a high benefit to patients.

Conclusions

Primary MSICHs are a rare occurrence. However, sporadic cases have continuously been reported worldwide. The majority of case reports come from Asian countries. MSICHs have many features in common with solitary intracerebral hemorrhage, including age and sex distribution, location of hematomas and mortality rate. Cases with bilateral basal ganglia hemorrhages have the worst prognosis and the highest mortality rate, whereas cases with bilateral thalamic hemorrhages have the highest unfavorable outcome rate. According to the present study, MSICHs have higher favorable outcome rates than primary solitary intracerebral hemorrhages. The supratentorial region is the most common site of bleeding, and no preponderance of the right side over the left side has been discovered. Primary MSICHs in the infratentorial region tend to occur in the cerebellum.

Disclosure Statement

The authors declare no conflicts of interest.

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Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

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114

Cerebrovasc Dis Extra 2014;4:102–114

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Laiwattana et al.: Primary Multiple Simultaneous Intracerebral Hemorrhages between 1950 and 2013: Analysis of Data on Age, Sex and Outcome

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