Heterotopic Ossification After Stroke: Clinical Profile and Severity of Ossification

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Background and purpose: The aim of this study was to evaluate heterotopic ossification (HO) prevalence after stroke, describing clinical features and investigating predictors of HO and its severity. *Methods*: A cross-sectional study was carried out in 7 rehabilitation centers (Sarah Network) from 2004 to 2013. *Results*: Among 17,794 stroke cases, 235 patients (1.3%) presented clinical and radiological evidence of HO. A log-binomial model with robust variance estimated the prevalence ratio of 1.3% in 10 years. A multinomial logistic regression was performed to investigate the predictors of HO and its severity. The presence of hemorrhagic stroke (prevalence ratio [PR] = 4.75; 95% confidence interval [CI] PR = 3.38; 6.68) and ischemic stroke with hemorrhagic transformation (PR = 3.08; 95% CI PR = 1.63; 5.81), male sex (PR = 1.60; 95% CI PR = 1.16; 2.22), spasticity (PR = 13.78; 95% CI PR = 8.59; 22.10), and cognitive impairment (PR = 1.88; 95% CI PR = 1.36; 2.60) were independently associated with HO. Patients with HO were younger ($P < .0001$) and presented a shorter time of disease ($P = .013$). Young adult patients were more likely to develop severe HO (odds ratio = 2.80, 95% CI 1.09; 7.20) than were elderly patients. Severe HO was also related to heavy alcohol consumption (2.45; 1.03-5.84) and involved 2 or more joints (5.34; 1.85-15.36). There was an association with use of invasive ventilation (6.30; 2.13-18.63) at the acute stroke phase and patients were dependent on activities of daily living after stroke (3.90; 1.00-15.19). *Conclusions:* Despite the small prevalence of HO after stroke, this 10-year multicenter study was able to identify several associated factors related to the management and severity of stroke as well as the hemorrhagic subtype.

Key Words: Stroke—heterotopic ossification—risk factors—correlation—prevalence

Heterotopic ossification (HO) is defined as ectopic bone formation around large joints, such as the hips, knees, elbows, and shoulders. HO is usually self-limited and associated with immobilization.[1,2] Its pathophysiology has yet to be determined. A growing body of evidence suggests that there is a complex interface between local and systemic conditions[3] that includes the autonomous nervous system and inflammatory responses, thereby inducing HO through the release of osteoinductive factors.[4-6] Prolonged immobilization, traumatic manipulation, spasticity, deep venous thrombosis, pressure ulcers, prolonged hospitalization in a critical care unit, and invasive ventilation are factors that are known to be related to HO genesis after trauma.[4-8] The occurrence of HO is relatively common in certain central nervous system lesions, such as cranioencephalic trauma (10%-23%) and spinal lesions (5%-50%).[3,4,9,10] Any insult to the central nervous system may lead to an injury in the blood brain barrier

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and favor the release of osteogenic factors.[11] In 1987, Berrol first mentioned that HO could occur after traumatic and vascular intracranial bleeding.[12]

The clinical spectrum of HO ranges from an incidental finding on X-rays to severe limitation of motion. Clinically significant HO around a joint is defined by pain and decrease in the range of motion with radiological evidence of abnormal bone formation. Both upper and lower extremities can be affected, with the most common joint implicated being the hip, in paretic limb.[3,13] The progression of HO may lead to complete ankylosis, functional disabilities, and negative impact on the rehabilitation process. The timing of its occurrence depends on the time of the diagnosis (whether based on clinical diagnosis or imaging). HO usually develops within the first month after neurological injury until several years, but is generally diagnosed between 1 and 6 months with a peak incidence in 2 months.[1,7,13,16] Unfortunately, medical interventions have limited effectiveness and the only actual treatment of HO is surgical excision.[1,4,13,21]

Ultimately, HO has been associated with other causes of upper motor neuron injury, such as stroke.[13,14] In stroke, HO prevalence seems to be as low as .5%-1.2% and this may contribute to the lack of knowledge about the epidemiological and clinical profile of HO after stroke.[15-18] This study aims to describe the clinical profile and factors associated with HO genesis and its severity in a large number of stroke patients who were admitted to a public network of rehabilitation hospitals over a 10-year period and finally to access if HO is increased by hemorrhagic stroke.

Methods

A cross-sectional study was performed from January 2004 to December 2013 among adult (18+ years old) stroke patients who were admitted in 7 rehabilitation centers. These centers were located in Northeast, Central, and Southeast regions in the country. All data included in the analysis were collected retrospectively based on electronic medical records.

We identified 477 patients with clinical and radiological evidence of HO among 19,659 stroke cases, until July 2015. After excluding other types of neurological issues, such as cerebral palsy, medullary lesions, brain lesions other than stroke, previous fractures or arthroplasty, osteomyelitis, another bone pathology, or Paget disease, 235 HO patients from 17,794 patients with stroke were included.

For the analysis, HO and HO severity were the dependent variables. The independent variables were demographic (sex, age), behavioral (current or previous histories of smoking and alcohol abuse), clinical (stroke subtype, pain, spasticity, number of joints, use of invasive ventilation), comorbidities (hypertension, diabetes, dyslipidemia, pressure ulcers), and sequelae (laterality, daily living activities, cognitive impairment, aphasia). The Ashworth scale assessed limb spasticity.[22] Functional Independence Measure was used to access daily living activities; grading categories in total independence, partially independence and total assistance.[23] Mini-Mental State Examination,[24-26] delayed recall of 10 simple figures,[27,28] clock drawing[29-31] were performed for cognitive assessment. Cut-off scores were adjusted for age and educational levels. Aphasia was evaluated separately, due to its imposing limitations.

HO severity was classified in the radiological evaluation of the affected joint, according to the criteria of Coelho and Beraldo, as mild, moderate, and severe; and severe cases were associated with ankylosis.[19]

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences Version 20.0. Data were displayed as means and standard deviation. Comparisons between groups were performed using a nonparametric test and a P value $\leq .05$ was considered statistically significant. A log-binomial model with robust variance estimated the prevalence ratio. Goodness-of-fit was measured using a deviance test. The factors associated with HO severity were investigated by multinomial logistic regression. Due a large sample size with a numerical disparity of the variables, a random sample of 60% of patients without HO was selected to construct a statistical model and 40% for validation, otherwise, we could have a bias where variables clinically insignificant emerge as relevant.

Ethical Approval

This study was approved by the local Research Ethics Committee (COEP, #869.467) in compliance with the principles of the Declaration of Helsinki. The board of Ethics Committee waived the need for written informed consent.

Results

The annual prevalence of HO remains approximately 1.3% per year over 10 years. We compared data from 17,559 stroke patients without HO to 235 patients with both diseases. Of those patients, hemorrhagic stroke was observed in 128, spasticity in 201 (85.5%), pain related to HO in 179 (76.2%), and cognitive impairment in 122 (51.9%). The most affected joints were hips (89.4%), followed by knees (15.7%), elbows (14.5%), and shoulders (8.5%). Correlation of the HO laterality had a clear predominance on the same side as the neurological sequelae. One hundred and ninety-five patients (83%) developed HO on the paretic side, 35 (14.9%) had bilateral HO, and only 5 (2.12%) presented on the side without motor sequelae. The majority of patients presented symptoms in a single joint (74.9%), received invasive ventilation (73.2%), were dependent after stroke (57.5%) and were incapable of walking

Table 1. *Demographic data—network rehabilitation hospital from 2004 to 2013*

	Stroke with HO ($n = 235$)	Stroke without HO ($n = 17,559$)	P value
Female/male	89 (37.9%)/146 (62.1%)	8544 (48.7%)/9015 (51.3%)	.001*
Age at stroke			
Mean ± SD	52.5 ± 13.2	58.7 ± 14.3	<.0001‡
Median (Q1; Q3)	51.8 (44.7; 60.8)	59.3 (49.6; 69.2)	
Stroke age: ≤60 y/>60 y	163 (69.3%)/72 (30.7%)	7858 (44.8%)/9701 (55.3%)	<.0001*
Ischemic/hemorrhagic	83 (35.3%)/128 (54.5%)	13,383 (76.2%)/3530 (20.1%)	<.0001*
Isch and hemorrhagic	24 (10.2%)	636 (3.68%)	
Time of stroke ≤ 18 months	231 (98.3%)	17362 (98.58%)	.528†
Time of stroke ≤ 24 months	235 (100)	17,406 (99.13%)	.182†
Time of stroke > 24 months	0	153 (.087%)	.012*
Spasticity	201 (85.5%)	12,833(73%)	<.0001*
Cognitive impairment	122 (51.9%)	6264 (35.7%)	<.0001*
Aphasia	77 (32.8%)	4749 (27%)	.057*
Smoking	102 (43.4%)	11,325 (64.5%)	.0121*
Alcohol abuse	75 (31.9%)	4568 (26%)	.037*
Hypertension	193 (82.1%)	14,674 (83,5%)	.588*
Dyslipidemia	101 (43%)	9103 (51.8%)	.007*
Diabetes	45 (19.1%)	5537 (31.53%)	<.0001*

Abbreviations: HO, heterotopic ossification; SD, standard deviation.
*Pearson's chi-squared test (asymptotic).
†Pearson's chi-squared test (exact).
‡Mann Whitney test.

(75.3%) and presented (98%) signs of HO until 18 months after their stroke. Table 1 shows the characteristics of the patients with stroke and HO.

Univariate analysis showed significant correlation ($P < .20$) with the type of stroke ($P < .001$), age ($P < .001$), sex ($P < .016$), time of stroke ($P < .001$), presence of diabetes ($P < .002$), dyslipidemia ($P < .017$), aphasia ($P < .028$), spasticity ($P < .001$), and cognitive impairment ($P < .001$; Table 2). After the multivariate analysis, HO after stroke was still significant ($P \leq .05$) and was associated with younger age, time of stroke, male sex, stroke subtype (hemorrhagic and ischemic with hemorrhagic transformation), spasticity, and cognitive impairment. Patients frequently develop HO in a short period after stroke ($P = .013$) and the probability to develop HO decreases as time passes after the neurological injury (prevalence ratio = .95; Table 3).

There was no association between HO and cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, smoking, and alcohol abuse. A multivariate log binomial model was adjusted to the data with .05 significance ($P = .074$).

The majority of patients presented moderate to severe HO (Table 4). Severe HO was 2.8 times higher among young patients and individuals who had HO in multiple joints. Invasive ventilation in acute stroke was associated with severe HO and the probability of ankylosis was 6.3 times higher (Table 5). Patients who were dependent on others to complete activities of daily living were 3.9 times more likely to have severe HO than other patients. Alcohol abuse was also associated with severe HO (odds ratio = 2.45, 95% confidence interval; Fig 1).

Discussion

To the best of our knowledge, this is the largest study to investigate patients with stroke who develop HO. We found the prevalence to be steady and low (1.3% per year), which was similar to findings in previous studies.[15-18] It is possible that with increasing stroke prevalence, the number of patients with HO might also increase. HO prevalence and severity seems to be related to several factors besides its subtype.

Similar to HO resulting from other lesions, the most affected joints were the hips, followed by the knees, elbows, and shoulders.[7,13] We also observed an absolute coincidence of HO on the same side as the neurological sequelae, as previously demonstrated.[16]

HO seems to be more prevalent and more severe in younger patients. We speculate that a more robust inflammatory response in this group might be partially responsible for this finding, which has also been observed in a spinal cord injury population.[9] The temporal relationship between the neurological injury and HO remains unclear. It is known that the phenomenon occurs at the earliest stages of neurological injury (within a month) and can last for years. In our case series, the HO incidence apparently decreases over time.[7,13,20]

The observed higher prevalence of HO in males has been reported.[4,9,19,21,32,33] Hormonal differences may be

Table 2. *Univariate logistic analysis of the associations between clinical variables and HO among patients with stroke admitted to the Network Rehabilitation Hospital from 2004 to 2013*

	Stroke with HO $n = 141$ (%)	Stroke without HO $n = 10,536$ (%)	PR	CI 95% PR	*P* value
Stroke					
Ischemic/hemorrhagic	11 (7.8)	392(3.7)	4.32	2.27; 8.21	<.001
	79 (56.0)	2133 (20.3)	5.65	3.98; 8.00	<.001
Hemorrhagic					
Age (years)					
Mean ± SD	52.2 (13.8)	58.8 (14.2)	.97	.96; .98	<.001
Median	51.8	59.3			
(Q1; Q3)	(43.7; 60.0)	(49.7; 69.2)			
Age ≤ 60 years	101 (71.6)	4709 (44.7)	3.12	2.16; 4.52	<.001
Sex					
Male	87 (61.7)	5422 (51.5)	1.51	1.08; 2.12	.016
Hypertension	115 (81.6)	8801 (83.5)	.86	.56; 1.31	.476
Smoking	55 (39.0)	3748 (35.6)	1.16	.83; 1.62	.398
Alcohol abuse	41 (29.1)	2726 (25.9)	1.17	.82; 1.68	.389
Diabetes	27 (19.1)	3377 (33.4)	.52	.34; .79	.002
Dyslipidemia	59 (41.8)	5481 (52.0)	.67	.48; .93	.017
More than one stroke	18 (12.8)	1380 (13.1)	.98	.60; 1.60	.931
Aphasia	50 (35.5)	2856 (27.1)	1.47	1.04; 2.07	.028
Time of stroke					
Mean (DP)	1.7 (2.3)	2.3 (4.0)	.95	.91; .99	<.001
Median	.9	.7			
(Q1; Q3)	(.4; 2.0)	(.3; 2.4)			
Spasticity	121 (85.8)	2845 (27.0)	15.73	9.82; 25.20	<.001
Cognitive impairment	76 (53.9)	3756 (35.6)	2.09	1.50; 2.90	<.001

Abbreviations: CI, confidence interval; PR, prevalence ratio.

Table 3. *Multivariate logistic analysis of the associations between clinical variables and HO among patients with stroke admitted to the Network Rehabilitation Hospital from 2004 to 2013*

Variable	HO (yes/no)$n = 141/n = 10,536$	PR	CI 95% PR	*P* value
Male	87/5422	1.6	1.16; 2.22	.004
Age at stroke				
Mean ± SD	52.2 ± 13.8 /58.8 ± 14.2			
Median (Q1; Q3)	51.8 (43.7;60.0)/ 59.3 (49.7;69.2)	.98	.97; .99	<.0001
Hemorrhagic stroke	79/2133	4.75	3.38; 6.68	<.0001
Isch/hemorrhagic	11/392	3.08	1.63; 5.81	.001
Spasticity	121/2845	13.78	8.59; 22.10	<.0001
Cognitive impairment	76/3576	1.88	1.36; 2.60	<.0001

Abbreviations: CI, confidence interval; PR, prevalence ratio.

an explanation as well as the genetic determination of bone mass, which is greater in males. Because stroke affects women after middle age, the reduction of estrogen associated with age and menopause would favor bone resorption and therefore may prevent HO.[34,35]

Similar to other studies related to HO in other diseases, spasticity was present in 85.5% of patients.[19,32,36-38] Mechanical tension at the tendon muscle junction during vigorous manipulations could be a source of microtraumas inducing local inflammation and the release of osteoblastic factors, which ultimately leads to HO[39] (Fig 2). On the other hand, the cross-sectional design of this study cannot exclude reverse causality, ie, HO increasing spasticity.[7]

Several studies have described a significant correlation between the severity of the neurological deficit and the severity of stroke in the acute phase. A key point of focus would be intensive care unit patients, who are often submitted to invasive ventilation.[8,40-44] Our study has demonstrated that 73.2% of all HO patients received this intervention and had an increased chance of developing severe HO (6.3 times).

Cognitive impairment after stroke may lead to worse functional recovery.[44] HO was associated with cognitive

Table 4. *Characteristics of the 235 patients with HO according to severity of the disease among stroke patients admitted to the Network Rehabilitation Hospital from 2004 to 2013*

	HO severity			
Number of cases (%)	Mild 68 (28.94%)	Moderate 115 (48.94%)	Severe 52 (22.12%)	*P* value
Age				
≤60 years	37 (22.7)†	85 (52.1)	41 (25.2)	.005*
>60 years	31 (43.1)††	30 (41.7)	11 (15.3)	
Gender				
Female	24 (27.0)	45 (50.6)	20 (22.5)	.842*
Male	44 (30.1)	70 (47.9)	32 (21.9)	
Stroke type				
Ischemic	33 (39.8)††	37 (44.6)	13 (15.7)	.015*
Isch/hemorrhagic	4 (16.7)	10 (41.7)	10 (41.7)††	
Hemorrhagic	31 (24.2)	68 (53.1)	29 (22.7)	
Number of joints				
One	62 (35.2)††	82 (46.6)	32 (18.2)†	.001**
Two	6 (11.5)†	30 (57.7)	16 (30.8)	
Three	0	3 (42.9)	4 (57.1)††	
Smoke				
No	38 (28.8)	68 (51.1)	27 (20.3)	.678*
Yes	30 (28.6)	47 (46.1)	25 (24.8)	
Pressure ulcer				
No	51 (33.6)	71 (46.7)	30 (19.7)	.095*
Yes	17 (20.5)	44 (53.0)	22 (26.5)	
Invasive ventilation				
No	32 (50.8)††	25 (39.7)	6 (9.5)†	<.001*
Yes	36 (20.9)†	90 (52.3)	46 (26.7)††	
Deambulation				
Independent	5 (45.5)	5 (45.5)	1 (9.1)	.420**
T cane	3 (37.5)	5 (62.5)	0 (.0)	
Elbow crutch	8 (36.4)	11 (50.0)	3 (13.6)	
Walking frame	6 (35.3)	9 (52.9)	2 (11.8)	
Wheel chair	46 (26.0)	85 (48.0)	46 (26.0)	
Cognitive impairment				
No	30 (26.5)	56 (49.6)	27 (23.9)	.686*
Yes	38 (31.1)	59 (48.4)	25 (20.5)	
Activity of daily living				
Independent	11 (35.5)	16 (51.6)	4 (12.9)	.108*
Partially independent	24 (34.8)	35 (50.7)	10 (14.7)	
Dependent	33 (24.4)	64 (47.4)	37 (27.6)	
Spasticity				
No	10 (29.4)	16 (47.1)	8 (23.5)	.967*
Yes	58 (28.9)	99 (49.3)	44 (21.9)	
Hypertension				
No	8 (19.5)	22 (53.7)	11 (26.8)	.319*
Yes	60 (31.1)	92 (47.7)	41 (21.2)	
Diabetes				
No	49 (26.8)	88 (48.1)	46 (25.1)†	.038*
Yes	18 (40.0)	23 (51.1)	4 (8.9)††	
Dyslipidemia				
No	34 (25.4)	63 (47.0)	37 (27.6)†	.054*
Yes	34 (33.7)	52 (51.5)	15 (14.9)††	
Alcohol abuse				
No	48 (30.2)	81 (50.9)	30 (18.9)	.196*
Yes	19 (25.3)	34 (45.3)	22 (29.3)	

*Pearson's chi-squared test (asymptotic).
**Pearson's chi-squared test.
†Adjusted residual < −1.96.
††Adjusted residual > +1.96.

Table 5. *Univariate logistic regression and multivariate logistic regression model for HO severity—comparison with mild HO*

Variable	Univariate – CI 95% OR*		Multivariate – CI 95% OR*	
	Moderate	Severe	Moderate	Severe
≤60 years	2.37 (1.26; 4.47) $P = .007$	3.12 (1.38; 7.08) $P = -.007$	2.05 (1.00; 4.21) $P = .052$	2.80 (1.09; 7.20) $P = .033$
Hemorrhagic stroke	1.96 (1.04; 3.68) $P = .038$	2.38 (1.05; 5.38) $P = .038$	NA	NA
Isch/hemorrhagic	2.23 (.64; 7.79) $P = .209$	6.35 (1.69;23.88) $P = .06$	NA	NA
Two or more joints	4.16 (1.64; 10.54) $P = .003$	6.46 (2.36;17.68) $P < .0001$	3.49 (1.34; 9.07) $P = .010$	5.34 (1.85; 15.36) .002
Pressure ulcer	1.86 (.96; 3.62) $P = .068$	2.20 (1.01; 4.79) $P = .047$	NA	NA
Invasive ventilation	3.20 (1.67; 6.13) $P < .001$	6.82 (2.57; 18.07) $P < .001$	2.65 (1.27; 5.50) $P = .09$	6.30 (2.13; 18.63) $P = .01$
Alcohol abuse	1.06 (.55; 2.06) $P = .863$	1.85 (.86; 3.98) $P = .114$	1.19 (.58; 2.45) $P = .631$	2.45 (1.03; 5.84) $P = .042$
ADL (dependent)	1.33 (.56; 3.20) $P = .519$	3.17 (.90; 10.90) $P = .068$	1.58 (.60; 4.17) $P = .352$	3.90 (1.00; 15.19) $P = .05$

Abbreviations: ADL, activities of daily living; OR, odds ratio.
Deviance test – $P = .176$.
*OR comparing with mild HO.

Figure 1. *Man, 53 years, hemorrhagic stroke with tetraplegia, prolonged ICU and invasive ventilation. Severe HO at right and moderate at left.*

impairment and may be related to the extent of brain injury. Additionally, severe conditions in the acute phase can delay rehabilitation and lead to chronic immobility and subsequent consequences. Activities of daily living-dependent patients are 3.9 times more likely to develop moderate and severe HO compared to other patients.

Study Limitations

This study has some limitations as well as selection bias. Its cross-sectional design prevents causality from being determined. In addition, the real prevalence of HO may be underestimated since only patients with clinical signs or symptoms received imaging studies, and asymptomatic patients may not have been diagnosed. Nevertheless, prospective studies may help identify HO genesis and risk factors for HO.

Conclusions

This study suggests that special attention should be provided to a specific stroke population that has a higher risk of developing HO, especially younger men with more severe vascular insults, such as hemorrhagic stroke, who have a history of invasive ventilation and who present cognitive impairment and signs of early spasticity. We suggest that those patients should have an early radiological exam in the joints on their paralyzed side. Cautious mobilization through passive and active exercises could also help avoid microtraumas and enhance movement

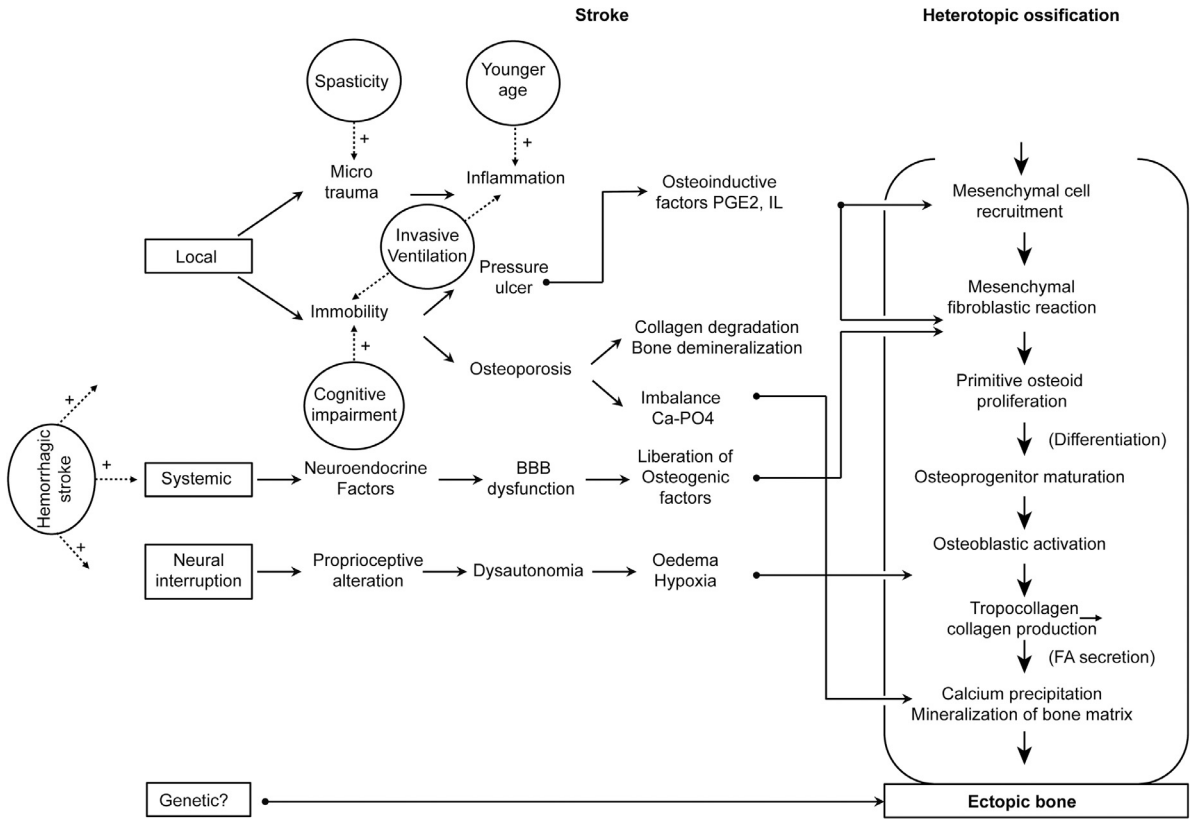

Figure 2. *Schematic figure adapted from van Kujik (2002). Proposed pathophysiology of HO in stroke. In the circles, risk factors associated with HO found in this study. Abbreviations: BBB, blood brain barrier; IL, interleucine; PGE2, prostaglandine E2.*

amplitude while preventing the need for additional treatments or surgeries.

A great barrier to treating HO is the relatively small amount of current knowledge about the disease. We hope this study contributes to advocacy for better diagnosis and prediction of risk factors related to HO.

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