

## **Title Page**

### **Stroke and Hypertension in Children and Adolescents**

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## **Abstract**

Hypertension is the single most important modifiable risk factor for adult stroke. Stroke mortality has significantly decreased over the last five decades; this decline has been mainly associated to improved blood pressure (BP) control. Although much less prevalent than in adults, stroke is an increasingly recognized cause of morbidity and mortality in children. Although hypertension has not been strongly identified as a risk factor in childhood stroke yet, there is preliminary evidence that suggests that elevated BP may be associated with stroke in children.

In this review, we summarized the literature that may link elevated BP to the development of childhood ischemic and hemorrhagic stroke. We suggest that elevated BP may be a significant risk factor that, alone or in combination with other multiple risk factors, leads to the development of stroke in childhood. We recommend that BP be measured and assessed carefully in every child presenting with acute stroke.

**Keywords:** Cerebrovascular, ischemic, hemorrhagic, blood pressure, pediatric

## I. Introduction

Hypertension is the single most important modifiable risk factor for stroke in adults.<sup>1</sup> In the past five decades, stroke mortality has significantly decreased from the third leading cause of death in the 1960s to the fifth cause in 2013.<sup>2</sup> This decline is mainly attributable to improved blood pressure (BP) control.<sup>3</sup>

Although much less prevalent than in adults, stroke is still one of the top ten causes of childhood death.<sup>2</sup> In children, multiple etiologies are associated with the development of stroke.<sup>4,5</sup> Although hypertension has not been strongly identified as a risk factor in childhood stroke to date, there is preliminary evidence that suggests that elevated BP may also be associated with stroke in children.

Hypertension has increased among children and adolescents in the last two decades, which parallels the current childhood obesity epidemics. The prevalence of hypertension is estimated to be three to four percent in children in general, but as high as ten percent in children with obesity.<sup>6-9</sup> Hypertensive children and adolescents develop subclinical target organ damage, such as left ventricular hypertrophy and carotid intimal thickness.<sup>10-13</sup> In addition, hypertension may affect the child's central nervous system, including retinal, cerebrovascular, and cognitive abnormalities.<sup>14-18</sup> Thus, the possibility that elevated BP might contribute to stroke in children should not be underestimated. We performed literature searches on three databases: PubMed, Embase and Web of Science. Our searches combined the concepts of stroke, brain ischemia, brain hemorrhage, and hypertension with the AND operator. The PubMed search

included Mesh terms and keywords. Our Embase search included Emtree terms and keywords. In addition, we included references from articles retrieved through these searches.

## **II. Epidemiology**

### ***Incidence of Childhood Stroke***

The incidence of childhood stroke has varied widely in the literature over the years,<sup>19-22</sup> from 2.5/100,000<sup>19</sup> to 13.5/100,000<sup>21</sup> children per year. On average, the combined incidence rates for ischemic and hemorrhagic stroke is 6.8/100,000.<sup>22</sup> The relative proportion of stroke type has also varied broadly; the ischemic to hemorrhagic stroke ratio has changed overtime from 0.33 to 2.67.<sup>19-22</sup> Early studies reported a higher proportion of hemorrhagic stroke;<sup>19,20</sup> more recent studies show higher rates of ischemic stroke.<sup>21,22</sup>

As traditional cardiovascular risk factors (such as obesity and hypertension) are becoming more prevalent among children at younger ages,<sup>6,23</sup> the incidence rates of childhood stroke may be rising as well.<sup>24</sup>

### ***Prevalence of Hospitalization for Stroke***

Hospitalization rates for ischemic stroke in children and young adults increased significantly from 1995 to 2008,<sup>25</sup> from 3.1 to 4.7/10,000 hospitalizations (51%) in five to 14 year-old boys, from 10.3 to 15.0/10,000 hospitalizations (45.6%) in 15 to 34 year- old males and from 3.5 to 4.3/10,000 hospitalizations (22.9%) in 15 to 34 year-old females; rates were unchanged in girls five to 14.<sup>25</sup>

The prevalence of hospitalization due to hemorrhagic stroke increased from 1.6 to 2.4/10,000 (50%; subarachnoid) and from 1.9 to 2.6/10,000 (36.8%; intracerebral) in boys and girls five to 14. In contrast, hospitalization rates for hemorrhagic stroke decreased in the 15 to 34 year-old group in general, mainly due to significantly lower rates in females (33% decreased for subarachnoid type).<sup>25</sup>

Hospitalization rates may increase as awareness of childhood stroke increases or because fewer children die pre-hospitalization. The latter may be the case for hemorrhagic stroke, although there are few population-based data, which include an estimate of mortality outside hospital.

### **III. Hypertension and Stroke: Definitions, Barriers and Limitations**

The standard definition of hypertension in children and adolescents is based on the normative distribution of blood pressure (BP) in healthy children; it is not based on clinical outcomes.<sup>26</sup> Hypertension is defined as a systolic BP and/or a diastolic BP equal or greater than the 95th percentile on repeated measurements. When the BP falls between the 90th and 95th percentiles, it is called prehypertension.<sup>26</sup>

Data on the impact of BP on stroke in children differ by the definition of high BP used. Some studies describing the association between BP and stroke in children included only children with the standard definition of hypertension above while other studies included children with elevated BP on just a single occasion,

not on repeated measures over time. For the purposes of this review, we have used the term “hypertension” for studies that included subjects who met the standard definition of hypertension and the term “elevated BP” for studies that also included subjects with high BP but did not necessarily have repeated measures over time.

Newer techniques, such as 24-hour ambulatory BP monitoring, are now available to establish and confirm the diagnosis of hypertension.<sup>27,28</sup> This procedure allows for a better assessment of BP changes, by providing measurements outside the office setting and by evaluating BP load (a measure of duration of BP elevation).

Both hypertension and prehypertension are under-recognized in the pediatric population.<sup>29</sup> BP is not measured in a significant proportion of ambulatory visits; hence, hypertension and prehypertension are likely to be undiagnosed in the pediatric stroke population, as well. Children may also have masked hypertension,<sup>30</sup> defined as a normal BP in the office but elevated in the out-of-office setting. Thus, in order to confirm masked hypertension, a 24-hour BP study would be necessary to confirm this diagnosis.<sup>31</sup>

Children and adolescents with severe BP elevation are at increased risk of neurologic adverse outcomes, including hypertensive encephalopathy and cerebrovascular accidents.<sup>14,32</sup> However, hypertension as a stroke risk factor, has been largely ignored in the pediatric literature.<sup>5</sup> Various stroke symptoms were reported in single patients or small case series with conditions where elevated BP was clearly associated with, or was an important risk factor in underlying conditions.<sup>31,33-44</sup>

We have identified multiple barriers to recognize the contribution of elevated BP to the development of stroke in childhood. Case series and review articles on pediatric stroke often did not mention elevated BP as a potential risk factor<sup>45,46</sup> (except in sickle cell disease, where it is a risk factor for both ischemic and hemorrhagic stroke).<sup>47</sup> Other stroke studies have not specified how the BP was obtained and interpreted or defined hypertension at much higher BP thresholds, underestimating its incidence.<sup>48-51</sup> In addition, there is no consensus regarding the timing of BP assessment; studies have defined hypertension at different time periods (i.e., at presentation, discharge, or follow up visit).<sup>4,49</sup> One study found that the BP was frequently abnormal, rarely measured and infrequently plotted on percentile charts.<sup>50</sup> Another study noted that BP assessment was suboptimal because height was inconsistently documented (as normal BP in children varies with different heights).<sup>26</sup> Other limitations included lack of controlled and serial measurements and under-reporting of specific risk factors.<sup>48,52</sup> McKay et al. suggested that hypertension prevalence might have been underestimated on the International Pediatric Stroke Study database, because there was no predetermined field on data entry sheet for modifiable adult risk factors.<sup>48</sup> Finally, large databases utilize ICD-9 and 10 discharge codes to identify subjects with hypertension; these are indeed administrative codes and not medical diagnosis. It is uncertain whether coding was appropriate and relevant in all cases.

#### **IV. Elevated BP and Ischemic Stroke**

Studies on pediatric ischemic stroke have increasingly identified a link with elevated BP (Table 1).<sup>4,5,25,32,48,49,53-59</sup> The prevalence of hypertension in ischemic stroke has been reported to vary between 5-65%, depending on how hypertension was defined. Kirkham et al. analyzed risk factors for arterial ischemic stroke and found that ten percent (8/83) with a first ischemic stroke or transient ischemic attack (TIA) were hypertensive. As hypertension was the only obvious factor in some of these cases, the authors suggested that hypertension could have played an etiologic role.<sup>5</sup>

George et al. reported an increase in the prevalence of classic cardiovascular risk factors among US adolescents and young adults hospitalized for ischemic stroke from 1995 to 2008. Hypertension, as a coexisting risk factor for stroke, increased from 25.3 to 37.2 percent ( $p < 0.001$ ) in 15 to 34 year-old males and from 19.2 to 32.2 percent ( $p < 0.001$ ) in same-age females.<sup>25</sup>

Ganesan et al. defined elevated BP if it was higher than the 90<sup>th</sup> percentile, including both hypertensive and prehypertensive subjects (Table 1).<sup>4,53</sup>

Interestingly, Collins et al. have argued that elevated BP, including prehypertension, may be detrimental at lower thresholds than the current guidelines. These investigators have suggested that statistical definitions should be reconsidered and that definitions be based on long-term cardiovascular risk.<sup>60</sup>

Hypertension has been associated with increased mortality in children hospitalized with ischemic stroke. In a retrospective review, Brush et al. determined the prevalence of hypertension in 84 children in the acute phase after

an ischemic stroke (Table 1).<sup>49</sup> The relative risk of death in the hospital was 1.7 times higher (95% CI =1.4-2.0; p = 0.05) and the one-year mortality 4.5 times higher (95% CI 0.6-34.5; p =0.096) in children with hypertension. Furthermore, hypertension (defined by ICD-9 codes for elevated BP or hypertension) was also associated with increased mortality (7.4% vs. 2.8%; p = 0.01) in the larger Kids' Inpatient Database; after adjusting for multiple covariates, hypertensive children had a 20% increased risk of mortality (odds ratio 1.2, 95% CI 1.1-3.3, p = 0.04).<sup>58</sup> These investigators also analyzed hospitalization rates for TIA in children<sup>57</sup> and found that hypertension (as defined above) was present in 33/531 (6.2%) cases of TIA, and in 8.1% of TIA subjects 15-18 years of age.<sup>57</sup>

## **V. Elevated BP and Hemorrhagic Stroke**

Elevated BP has also been identified as a risk factor for intracerebral hemorrhage in children as well. The prevalence of hypertension varied from 3.4 to ten percent in various hemorrhagic stroke series (Table 2).<sup>51,54,61-65</sup> Hypertension was found in 2/30 (6.6%) subjects from six months to 19 years of age with non-traumatic cerebral hemorrhage, regardless of whether there was a vascular abnormality.<sup>51</sup> Of note, hypertension was defined as a BP of 160/95 across all ages, a BP that is much higher than the BP thresholds that characterize hypertension in children.<sup>26</sup> This definition would underestimate the prevalence of hypertension in children.

## **VI. Elevated BP and Recurrent Strokes**

Hypertension has been recently identified as a risk factor for recurrent strokes in childhood cancer survivors.<sup>66</sup> Data was obtained from the Childhood Cancer Survivor Study, a retrospective cohort study; hypertension independently predicted recurrent stroke (hazard ratio 1.9; 95% CI 1.0-3.5;  $p = 0.052$ ). Stroke type (ischemic or hemorrhagic) and definition of hypertension were not reported. In contrast, hypertension (defined as BP >90<sup>th</sup> percentile) was not a significant predictor of recurrent clinical stroke or reinfarction in either the whole or the cryptogenic group in the Great Ormond Street series.<sup>67</sup>

## **VII. Stroke and Sickle Cell Disease**

Sickle cell disease is an autosomal recessive disease with a high risk of overt ischemic and hemorrhagic cerebrovascular accidents.<sup>68</sup> Untreated sickle cell disease is the most frequent cause of childhood stroke;<sup>69</sup> some children present with 'silent' infarctions detectable on MRI and associated with cognitive difficulties.<sup>70</sup>

There is now increasing interest in elevated BP as a risk factor for stroke in sickle cell disease. Elevated systolic BP was associated with an increased incidence of both overt and silent cerebral infarction.<sup>71-72</sup> A history of hypertension was also linked to increased risk in hemorrhagic stroke.<sup>73</sup>

Although BP has been typically reported to be lower than in the general population, children with sickle cell disease were found to have abnormal BP patterns.<sup>74-76</sup> In a cross-sectional review, 8/48 (16.7%) children with sickle cell disease had elevated BP (prehypertension or hypertension).<sup>74</sup> Utilizing 24-hour

BP monitoring criteria<sup>27,28</sup>, 18/52 (35%) of patients had previously unrecognized hypertension, 9/52 (17%) had pre-hypertension and 29/52 (56%) lacked the normal nocturnal dip in BP. In addition, masked hypertension was found to be prevalent in the sickle cell population.<sup>76</sup> While only 4/38 (10.3%) children with sickle cell disease were hypertensive based on clinic BP, 17/38 (43.6%) had ambulatory hypertension confirmed by 24-hour BP measurements. Lastly, a large national database showed a significant increase in hypertension (defined by discharge codes) as an important comorbidity, from 1.5 percent in 1997 to 11.5 percent in 2006 in children with sickle cell hospitalized with stroke.<sup>77</sup>

### **VIII. Stroke and Genetic Disorders**

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor suppressor syndrome characterized by histologically benign tumors of the peripheral and central nervous system, as well as the skin. Patients with NF1 have an increased risk of cerebrovascular disease. The odds of stroke are significantly increased for both adult and pediatric subjects with NF1 compared with the general population.<sup>78</sup> The risk is higher for hemorrhagic strokes (odds 1.9;  $p < 0.0001$ ), although it is also increased for ischemic strokes in children (odds ratio, 3.4;  $p < 0.0001$ ). Pediatric patients were more likely to have hypertension. In addition to being hypertensive as part of their disease (related to the presence of neurofibromin in aortic smooth muscle),<sup>79,80</sup> patients with NF1 may have secondary peripheral vasculopathy, like renal artery stenosis or renal moyamoya predisposing to hypertension. The development of a pheochromocytoma is

another risk factor predisposing to hypertension and, in selective cases, to stroke.<sup>42</sup>

Tuberous Sclerosis Complex (TSC) is an autosomal-dominant neurocutaneous disease characterized by widespread hamartomas and benign or rarely malignant neoplasms affecting various organs.<sup>81,82</sup> Renal involvement is present in more than 50% of cases, most commonly renal angiomyolipomas or cysts.<sup>81,82</sup> About 2% to 3% of these patients have bilateral polycystic kidney, because of mutation of two adjacent genes on chromosome 16, which is diagnosed in infancy or early childhood.<sup>83</sup> Furthermore, hypertension is a well-known complication of TSC mainly caused by renal cyst involvement or angiomyolipomas.<sup>82</sup> More rarely, hypertension may be secondary to renovascular occlusion or aortic aneurysm.<sup>84</sup> Although a wide variety of central nervous system abnormalities are associated with TSC, intracerebral hemorrhage and hemorrhagic stroke are rare.<sup>85</sup> In most of the reported cases, it is associated with either underlying cerebrovascular malformation, like ectasia, aneurysm and arteriovenous malformation or hemorrhage into the subependymal giant cell astrocytoma.<sup>86-88</sup>

Fabry disease, an inherited disorder caused by deficiency of alpha-galactosidase A activity, is associated with high morbidity and mortality related to renal, cardiac, and cerebrovascular disease, which are also important outcomes in patients with elevated blood pressure.<sup>89-91</sup> Among cardiovascular manifestations of Fabry disease there is a high prevalence of uncontrolled hypertension, left ventricular hypertrophy, rhythm and conduction abnormalities, increased intima media thickness, valvular insufficiency, and ischemic heart disease.<sup>92,93</sup> Vital organ

function progressively declines over time, placing patients with Fabry disease at risk of developing renal failure, cardiovascular dysfunction, and stroke.<sup>93,94</sup>

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development and progressive enlargement of cysts in the kidneys, and a multitude of extra renal manifestations, including the development of intracranial aneurysms. Subarachnoid hemorrhage from a ruptured aneurysm is one of the most serious complications, which can occur in children as well.<sup>95-97</sup>

## **IX. Stroke and Drug Use and Abuse**

Several drugs -both licit and illicit- have been associated with both hypertension and stroke.<sup>98-104</sup> Stroke related to over-the-counter cough and cold drugs (such as phenylpropanolamine and pseudoephedrine) was associated with acute hypertension and/or vasospasm or angiitis.<sup>98</sup> Prescription stimulants may be associated with adverse cardiovascular events, including stroke and hypertension<sup>105,106</sup>. However, a systematic review did not find an association between stimulant use and adverse cardiovascular outcomes in six of seven population-based observational studies in children.<sup>99</sup>

Cocaine and amphetamines are the illicit drugs more strongly linked to stroke.<sup>102</sup> Hypertension plays an important role in stroke mechanism for both illicit drugs. Both ischemic and hemorrhagic stroke are more common in cocaine and amphetamine users. However, hemorrhagic strokes are more frequent with amphetamine use, up to twice the risk of cocaine (odds ratio 4.95 vs. 2.33).<sup>103,104</sup>

Marijuana, the most commonly used illicit drug in the US, may be also associated with acute cerebrovascular events.<sup>102,107,108</sup> A recent population-based analysis demonstrated that marijuana use was associated with 17% increased risk of hospitalization for acute ischemic stroke.<sup>108</sup>

## **X. Stroke and Sleep Apnea**

Sleep disordered breathing, including, snoring, sleep apnea and nocturnal hypoxemia, is a recognized risk factor for adverse cardiovascular outcomes, including hypertension and stroke in adults<sup>109</sup> and there is some evidence for a link to hypertension in children.<sup>110</sup>

There are few data on whether there is an association between sleep-disordered breathing, hypertension and stroke in children in the general population, in whom the prevalence of this breathing disorder is less than 5%. Children with sickle cell disease appear to have a higher prevalence (higher than 10%) of sleep-disordered breathing, and there have been case reports of stroke in children with sickle cell disease and obstructive sleep apnea, although whether any link involves hypertension remains uncertain.<sup>111-113</sup> In addition, there is evidence that children with sickle cell disease with a mean overnight oxygen saturation of less than 96% are more likely to have a central nervous system event than those with mean overnight oxygen saturation higher than 96%.<sup>114</sup> Adenotonsillectomy appears to reduce stroke risk in sickle cell disease, but it is not known whether this is associated with a reduction in BP.<sup>115</sup>

Recently several groups have looked into whether the mechanism linking stroke and sleep-disordered breathing might involve an increase in TCD velocities and if so, whether the association is with obstructive sleep apnea or with chronic oxygen desaturation. TCD velocities were higher than controls in mild obstructive sleep apnea in the general pediatric population, but there was no difference in systolic or diastolic BP.<sup>116</sup> TCD velocities normalized around a year post-adenotonsillectomy, but BP was not reported and these neurologically normal children were not followed up long term for stroke risk.<sup>117</sup>

Goldstein et al. tested the association between polysomnography and TCD outcomes in a cohort of children 2 -14 years old with sickle cell disease and did not find an association with history of snoring, polysomnography and TCD velocities.<sup>118</sup> Three children had follow-up TCD recordings six weeks, four and six months post-adenotonsillectomy; TCD velocities did not significantly decrease in any child. Bader-Meunier reported two children with snoring and sickle cell disease in whom abnormal velocities (higher than 200 cm/sec) reduced into the normal range (lower than 170 cm/sec),<sup>119</sup> but there was no evidence that adenotonsillectomy reduced TCD velocities in the larger London series.<sup>120</sup> None of these studies documented BP. There was no evidence of reduction of TCD velocities or BP in a six week trial of auto-adjusting continuous positive airways pressure (auto-CPAP) in children with SCD,<sup>121</sup> but these will be important outcomes in the current Phase II trial of six months of auto-CPAP compared with standard care.<sup>122</sup>

## **XI. Hypertension and Cognition and Potential Implications for Neurovascular Health**

There is emerging, preliminary evidence that children with hypertension manifest cognitive differences when compared to normotensive controls. These preliminary studies consist mostly of database and single-center studies that focus primarily on differences in neurocognitive test performance and differences in cerebrovascular reactivity between hypertensive and normotensive subjects.<sup>123</sup> Using data from participants in NHANES III, investigators evaluated the neurocognitive test performance of children aged 6-16 years with elevated systolic BP ( $\geq 90^{\text{th}}$  percentile) to that of participants with normal systolic BP. Elevated systolic BP was independently associated with lower Digit Span scores, a measure of working memory and attention.<sup>124</sup> In a subsequent prospective, small, single-center pilot study, investigators showed that children with sustained hypertension had worse executive function compared with normotensive controls, as measured by a parental rating scale.<sup>125</sup> Furthermore, executive function scores in the hypertensive group improved after 12 months of antihypertensive medication.<sup>126</sup> In addition, Adams et al. showed that children with hypertension are more likely to be diagnosed with a learning disability, suggesting that they are at increased risk for academic difficulties.<sup>127</sup> While the physiologic basis of the neurocognitive test performance deficits in children with hypertension is not known, pediatric hypertension has been associated with alterations in cerebrovascular reactivity, the capacity of the cerebral blood

vessels to dilate in response to different stimuli, suggesting possible effects of hypertension on the cerebral vasculature.<sup>15</sup>

Findings of studies in adults raise concern for the neurovascular implications of the above cognitive effects of hypertension in youth. There is evidence that hypertension from young adulthood effects subsequent cognitive decline. In a 20-year longitudinal study, Elias et al. examined the relationship between hypertension and cognitive decline. The investigators found that young hypertensive adults (mean age, 34.9 years) were just as susceptible to subsequent BP-associated cognitive decline as were older adults.<sup>128</sup> Moreover, there is evidence that decreased performance on neurocognitive testing is an early manifestation of vascular disease that predicts incident stroke. In the Atherosclerosis Risk in Communities Study, middle-aged participants with cognitive test scores in the lower quartile had a significantly higher incidence of stroke over a median follow-up period of 6.4 years compared with subjects with scores in the highest quartile ( $p = 0.007$ ).<sup>129</sup> Taken together, these observations underscore the potential impact of early onset hypertension on neurocognitive function, subsequent cognitive decline, and incident stroke.

## **XII. Conclusions and Recommendations**

In this review, we critically assessed whether there is a link between stroke and elevated BP in children, and noted many barriers and limitations that have delayed recognition of a possible association. Hypertension is under-recognized in the general pediatric population and likely in the pediatric stroke population as

well.

Although hypertension has not been strongly identified as a risk factor in childhood stroke to date, it is possible that elevated BP plays a role in its pathophysiology. We presented preliminary evidence that may link elevated BP to the development of ischemic and hemorrhagic stroke in children. Hence, elevated BP may be a significant risk factor that, alone or in combination with other risk factors, leads to the development of childhood stroke.<sup>5,64</sup>

The American Stroke Association<sup>130</sup> has advocated control of hypertension in childhood hemorrhagic and ischemic stroke, but specific recommendations are lacking. We recommend that BP be assessed and correctly measured in all children with suspected or confirmed acute stroke. Measurement and timing of BP assessment should be standardized.

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## **Author Contribution**

Dr. Kupferman substantially contributed to conception and design and drafted the manuscript.

Drs. Zafeiriou, Lande and Kirkham contributed to acquisition, analysis or interpretation of the data, and critically revised the manuscript for important intellectual content.

Dr. Pavlakis substantially contributed to conception and design and critically revised the manuscript for important intellectual content.

All five coauthors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## **Disclosures**

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## **Ethical Approval**

Not applicable for topical review

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**Table 1. First Ischemic Stroke and Elevated Blood Pressure in Children and Adolescents <20 years of age**

<b>First Author (reference)</b>	<b>Year</b>	<b>Study design</b>	<b>Population</b>	<b>Definition</b>	<b>Prevalence of Elevated BP and/or Hypertension</b>
***Kirkham (5)	2000	Retrospective  Single center	Not  specified	Not specified	8/83 (10%) with "hypertension"
**Ganesan (53)	2002	Retrospective  Prospective  Two centers	21 days-  <20 years	BP >90th percentile  (includes prehypertension)	9/22 (41%) had "elevated BP"
**Ganesan (4)	2003	Retrospective  Prospective  Single center	21 days-  <20 years	BP >90th percentile  (includes prehypertension)	104/208 (50%) had "elevated systolic BP" 78/208 (37.5%) had "elevated diastolic BP"
***Lo (54)	2009	Retrospective  Database	1 month-  20 years	ICD-9 codes for  hypertension	172/3,156 (5.4%) with "hypertension"

*Bigi (55)	2011	Prospective Database	1 month- 16 years	BP $\geq$ 95 <sup>th</sup> percentile at discharge or preadmission history of hypertension	4/128 (5%) with “hypertension” or “history of hypertension”
*Brush (49)	2013	Retrospective Single center	1 month- 18 years	BP $\geq$ 95 <sup>th</sup> percentile	19/84 (22%) had “hypertension” for 3 days
***Adil (58)	2015	Retrospective Database	1 month- 18 years	ICD-9 codes for elevated BP and hypertension	156/2,590 (6%) had “elevated BP or hypertension”
***Grelli (59)	2016	Retrospective Single center	1 month- 18 years	BP $\geq$ 95 <sup>th</sup> percentile	64/98 (65%) with “hypertension”

BP = blood pressure

\* hypertension assessed according to standard definitions

\*\* study included pre-hypertension and hypertension

\*\*\* study did not provide details how hypertension was diagnosed or defined (discharge diagnoses codes are included in this category)

**Table 2. Non-traumatic Hemorrhagic Stroke and Hypertension in Children and Adolescents <20 years of age**

First Author (reference)	Year	Study design	Population	Definition	Prevalence of Elevated BP
***Livingston (61)	1986	Retrospective Single center	1 month- 16 years	Not specified	1/27 (4%) with "hypertension"
****Awada (51)	1998	Retrospective Multicenter	birth - <10 years 10 -19 years	BP ≥160/95	1/12 (8%) with "hypertension" 1/18 (6%) with "hypertension"
***Meyer-Heim (62)	2003	Retrospective Single center	1 month- <18 years	Not specified	3/34 (9%) with "hypertension"
***Fullerton (63)	2007	Retrospective Database	1 month- <20 years	Not specified	4/116 (3.4%) with "hypertension"

*Lo (64)	2008	Retrospective Single center	birth -17 years	BP >90th percentile	38/85 (45%) with “elevated BP” at presentation  3/22 (14%) with “elevated BP” at follow-up
***Lo (54)	2009	Retrospective Database	1 month- 20 years	ICD-9 codes not specified	124/2,022 (6.1%) with “hypertension”
***Jordan (65)	2009	Retrospective Single center	birth -18 years	Not specified	3/30 (10%) with “hypertension”

BP = blood pressure

\* hypertension assessed according to standard definitions

\*\* study included pre-hypertension and hypertension

\*\*\* study did not provide details how hypertension was diagnosed or defined (discharge diagnoses codes are included in this category)

\*\*\*\* hypertension defined at much higher levels than current guidelines