

# **Neuropsychological function in children with hemophilia: A review of the Hemophilia Growth and Development Study and introduction of the current eTHINK study**

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**Abbreviations:**

ADHD	Attention-Deficit/Hyperactivity Disorder
CBCL	Child Behavior Checklist
CG	Coordination and Gait
CHQ	Child Health Questionnaire
CPT	Continuous Performance Test
eTHINK	Evolving Treatment of Hemophilia's Impact on Neurodevelopment, Intelligence and Other Cognitive Functions
FAM	Family Assessment Measures
HGDS	Hemophilia Growth and Development Study
HIV	Human Immunodeficiency Virus
HTC	Hemophilia Treatment Center
ICH	Intracranial Hemorrhage
LD	Learning Disability
MRI	Magnetic Resonance Imaging
PBRS	Pediatric Behavior Rating Scale
CHQ-PhS	Child Health Questionnaire Physical Health Summary
PIC-R	Personality Inventory for Children - Revised
QRS	Questionnaire on Resources and Stress
SD	Standard Deviation
SS	Standard Score
UK	United Kingdom

US United States

WIAT Wechsler Individual Achievement Test

WRAT-R Wide Range Achievement Test - Revised

## **Abstract**

Almost all of what is known about neurologic and cognitive development in hemophilia derives from the Hemophilia Growth and Development Study, conducted during an era when treatment regimens and comorbidities differed significantly from the current environment. Results suggested hemophilia and HIV had independent effects and hemophilia negatively impacts academic achievement, attention, and behavior. The introduction of prophylaxis treatment in hemophilia has created the need for a re-evaluation of the effects of hemophilia on neurodevelopment and cognition. We outline the Evolving Treatment of Hemophilia's Impact on Neurodevelopment, Intelligence and Other Cognitive Functions (eTHINK; NCT03660774) study, which aims to meet this need.

## **Introduction**

Congenital hemophilia is a rare, X-linked bleeding disorder caused by genetic mutations resulting in a deficiency of either clotting factor VIII (hemophilia A, 80%) or factor IX (hemophilia B, Christmas disease, 20%). This condition is characterized by internal bleeding into the joints, muscles, and other tissues (including intracranial hemorrhage), which can cause severe pain, joint damage, and disability. Hemophilia is classified as mild, moderate, or severe, depending on the amount of clotting factor in the person's blood.<sup>1</sup>

Incorporation of routine prophylactic factor replacement therapy, starting in early childhood for severe disease, now allows patients with this disorder to participate in many more physical activities<sup>2,3</sup> and has reduced missed school and work time.<sup>4,5</sup> However, despite the more widespread use of factor replacement therapy to limit symptoms of physical disability in children with severe hemophilia, little is known about the impact of the disease on their cognitive development. In theory, children with hemophilia might be at risk of long-term cognitive and behavioral symptoms due to both disease-specific mechanisms, such as cumulative cerebral microbleeds, and more general psychosocial stressors related to chronic illness that are not addressed by routine factor replacement.

Here we will review what is known about neurologic and cognitive development in hemophilia, almost all of which derives from studies conducted during an era when treatment regimens and comorbidities (principally HIV/HCV infection) differed significantly from the current environment. We will then outline a novel proposal to investigate the impact of hemophilia on neurodevelopment under current standards of care.

### **Hemophilia Growth and Development Study (HGDS)**

In the early 1990s, HGDS formally examined the impact of hemophilia on neurodevelopment, including executive functions and intelligence. Funded by the Centers for Disease Control and Prevention, the National Institutes of Health, and the Maternal and Child Health Bureau of the Health Resources and Services Administration, HGDS was a 4-year observational study initiated in 1988 that was specifically designed to understand the effects of HIV on children and adolescents with moderate to severe hemophilia in the United States. The analysis population

included 333 participants born between 1970 and 1982, aged 6 to 18 years at baseline, of whom 207 (62%) were HIV-positive. For some analyses, siblings without hemophilia were used for comparison purposes. HGDS included comprehensive baseline growth, neurologic, immunologic, neuropsychological examinations, and imaging.<sup>6</sup>

Baseline evaluations in HGDS revealed several neurologic, neurocognitive, and radiologic findings (**Table 1**).

**Neurologic examination** commonly revealed abnormalities: abnormal cranial nerve function (11%), abnormal deep tendon reflexes (17%), abnormal strength (23%), abnormal coordination (25%), and abnormal muscle tone, bulk, or joint range of motion (31%). Results indicated that moderate-severe hemophilia correlated with substantial neurologic dysfunction and that certain findings, such as abnormal reflexes or decreased muscle bulk, could reflect neurologic consequences of HIV infection.<sup>7</sup>

**Neuropsychological testing** at baseline revealed that HIV-positive participants were 50% more likely to show scores ~1 SD below the expected range for age in at least 3 of 9 functional areas compared with HIV-negative participants ( $p = 0.051$ ).<sup>6</sup> Neurodevelopmental assessment did not show statistically significant differences between HIV-positive and HIV-negative participants at baseline. The proportion of participants exhibiting below-average performance in three or more areas assessed was about 25% overall. For both groups, mean test scores were within the average range for age; however, academic and adaptive skills were lower than expected, and more behavioral/emotional problems were reported compared to published norms. The HIV-positive participants were relatively free of HIV-related neuropsychological

impairment at baseline, suggesting that observed differences with the general population may have been related to moderate-severe hemophilia.<sup>8</sup> Attention and information processing are functions that are often found to be sensitive to diffuse injury to the central nervous system, including HIV-associated neurodegeneration and also potential injury related to hemophilia (e.g., intracranial hemorrhage). Two measures sensitive to attention deficits were used: Continuous Performance Test (CPT) and the Span of Apprehension (Span). CPT results revealed subtle difficulties with sustained attention and possible impulsivity issues in the HIV-positive group. Span scores were associated with the presence of a prior intracranial hemorrhage (ICH) but were not sensitive to HIV status or degree of immune suppression in the HIV-positive children, suggesting morbidity related to the prior bleed event.<sup>9</sup>

**Neuroimaging** included baseline brain magnetic resonance imaging (MRI) in 310 subjects and demonstrated multiple acquired lesions, including old hemorrhagic lesions and non-hemorrhagic lesions such as infarction; congenital abnormalities were uncommon. Diffuse cerebral atrophy appeared to be associated with HIV infection and was mostly observed in participants with compromised immunologic function.<sup>10</sup> MRIs in HIV-negative males showed abnormalities, some of which were determined to be congenital. Eighteen percent of participants had acquired lesions possibly related to hemophilia or its treatment.<sup>10,11</sup> A comparison of study participants' MRI scans with those of their unaffected siblings demonstrated that focal white matter lesions on T2 images were an incidental finding occurring in both groups.<sup>12</sup>

**Relationship between neurologic, neuropsychological, and MRI findings** was investigated using least squares modelling to assess neuropsychological scores by

HIV status, age, and baseline neurologic findings, adjusting for environmental and medical history variables. Variables associated with lower neuropsychological performance included academic problems, coordination and/or gait abnormalities, parents' education, and previous head trauma. The analysis concluded that hemophilia-related complications have a subtle adverse influence on cognitive performance. HIV infection was not associated with neuropsychological dysfunction in this group even when MRI abnormalities were present.<sup>13</sup>

Over the 4-year follow-up period, longitudinal findings of the HGDS included the following results from neurologic examination, neuroimaging, and neuropsychological assessment.

**Neuropsychological findings over time were evaluated in relation to declining or stable immune function.**<sup>14,15</sup> There were significant differences briefly described below over time in nonverbal intelligence, perceptual/performance skills, nonverbal memory, academic achievement, and language, most noticeable in those with low CD4 counts. On measures that are known to show a practice effect for repeated measures, scores were stable in those with low CD4 counts, suggesting opposing positive effects of practice and HIV-related decline. Weaker academic performance relative to IQ was found in all groups. Based on the analysis, hemophilia itself was identified as a potential risk factor for academic underachievement.<sup>14</sup> Caregivers completed the Vineland Adaptive Behavior Scales and Pediatric Behavior Rating Scale (PBRS) to assess adaptive behavior and emotional and behavior problems. Vineland Communication scores declined in those with low CD4 counts; baseline PBRS Attention Deficit and Deviation symptoms were more prevalent and decreased more sharply in this group. Low CD4 counts were associated with more PBRS

Health and Depression-Anxiety symptoms. Changes in these areas appeared to be related to immune functioning.<sup>15</sup>

**Neurocognitive and academic findings were assessed longitudinally in relation to hemophilia morbidity**, as measured by abnormalities in coordination and gait (CG), likely reflecting impact of recurrent hemarthrosis on joints in patients with more severe disease. Of 333 enrolled participants, 307 (92.2%) had complete data for all items, and of these, 153 (49.8%) had normal CG, 126 (41.0%) were classified as having transiently abnormal CG on the basis of one or more (but less than five) abnormal CG examination findings, and 28 (9.1%) had permanently abnormal CG. In addition, patients with hemophilia and inhibitors were 2.8 times more likely to have abnormal CG compared with those patients without inhibitors.<sup>16</sup>

Academic problems were reported at baseline for 96 (31.3%) participants in the group. Although participants performed within the average range for age on measures of intellectual ability, there were significant differences between CG outcome groups at baseline and throughout the 4 years of study. Participants with no CG abnormalities had higher Wechsler IQ scores than those with abnormal CG at baseline, and analysis of Wechsler subtests showed significant cross-sectional and longitudinal associations between CG and scaled scores on Information, Similarities, Arithmetic, Vocabulary, Digit Span, and Coding/Digit Symbol subtests. Participants without CG abnormalities consistently achieved higher scores than those with CG abnormalities on Reading, Spelling, and Arithmetic subtests of the Wide Range Achievement Test–Revised (WRAT-R), suggesting a relationship between lower achievement and the functional severity of hemophilia. For participants without academic problems, those with normal CG achieved higher mean scores in Reading,



Spelling, and Arithmetic (approximately 8 standard score (SS) points higher across the 5 examinations) than those with abnormal CG. Analysis suggested that lower academic achievement is related to the functional severity of hemophilia, reflecting the degree to which hemophilia interferes with the ability of these children and adolescents to interact with their environments and to access opportunities for development. The observed differences indicate a fairly large downward deviation from population mean scores in both intelligence and achievement for the children who appear to be most affected by hemophilia morbidity.<sup>16</sup>

**Neurologic evaluation through four annual assessments** included logistic regression to examine at study conclusion the relationship between neurologic findings, HIV status, CD4 cell counts, and vital status. The risks of non-hemophilia-associated muscle atrophy, behavior change, and gait disturbance increased over time in immune-compromised HIV-positive compared with HIV-negative or immunologically stable HIV-positive participants. The risk of behavior change in immune-compromised HIV-positive participants rose to 60% by year 4 (vs 10%-17% for other HIV groups analyzed). Forty-five HIV-positive participants died; participants who died had increased rates of hyperreflexia, non-hemophilia-associated muscle atrophy, and behavior change. Analysis demonstrated a high rate of neurologic abnormalities in HIV-positive participants over time. Hemophilia per se was associated with progressive abnormalities of gait, coordination, and motor function.<sup>17</sup>

**In the Family Stress and Coping Study**, which was run as an adjunct to HGDS, the caregivers of 162 males completed three youth and family questionnaires (Personality Inventory for Children-Revised [PIC-R]; Questionnaire on Resources and Stress [QRS]; and Family Environment Scale). Results suggested that

caregivers perceive psychosocial problems in HIV-positive youths with hemophilia and their families; some problems were specifically associated with greater immune compromise.<sup>18</sup>

### **Additional Studies (Table 1)**

Although HGDS clearly identified HIV and hemophilia as independent factors affecting neurologic and neurocognitive function and development, and many studies have identified psychosocial issues in children with hemophilia, there are limited published subsequent studies focused on specific concerns for neurocognitive function, and none of these are recent.

Three studies suggest a higher prevalence of ADHD and learning disabilities than the general population. As an early study in the HIV era, the Pennsylvania State University (Hershey Medical Center) study examined the relationship of HIV status, type of hemophilia, and school absenteeism to cognition, educational performance, mood, and behavior. Assessments (**Supplemental Table S1**) found that mean IQ was higher than expected for age, and the rate of enrollment in gifted programming among study participants was 2.4 times higher than the statewide average.

However, the study reported a disproportionately high prevalence of attention deficit hyperactivity disorder (ADHD; 28.3%), learning disability (LD; 15.8%), and graphomotor weakness not related to HIV status or hemophilia severity. Participants had a high rate of absenteeism, but this was not associated with academic achievement, IQ, or ADHD/LD diagnoses.<sup>19</sup> In an initial study of two dimensions of ADHD (inattention and hyperactivity) at the Phoenix Children's Hospital, 29% of the 34 males with hemophilia had pre-study ADHD diagnoses assigned by health care providers outside the HTC and 38% were participating in special education. Parent

rating scales showed that 26% of the participants exceeded the cutoff for ADHD inattentive type, 18% for ADHD hyperactive/impulsive type, and 18% for ADHD combined type.<sup>24</sup> In a follow-up study in Phoenix, assessments (**Supplemental Table S1**) found that males with hemophilia were rated significantly higher on dimensions of hyperactivity and inattention by teachers, and on hyperactivity by parents. Males with hemophilia also committed significantly more impulsive errors on the standardized tests. Despite this trend, only one child with hemophilia met diagnostic criteria for ADHD.<sup>25</sup> In the context of earlier studies,<sup>19</sup> the authors suggested that males with hemophilia are at risk for ADHD-spectrum problems, and that despite falling short of meeting diagnostic criteria for ADHD, they likely struggle with impulsivity issues.<sup>25</sup>

Two studies in the 1990s focused specifically on intelligence (IQ) and academic achievement. Toronto's Hospital for Sick Children published (1997) a longitudinal investigation of neuropsychological functioning in children and adolescents with hemophilia and HIV infection, hemophilia only, and their siblings using a 4- to 6-hour test battery typically completed in two sessions on the same day. All three groups showed weaker academic achievement than expected based on levels of intellectual performance; however, no differences related to HIV status were observed. The authors concluded that HIV-positive children with hemophilia did not show a progressive pattern of neuropsychological impairment.<sup>20</sup> The Academic Achievement in Children with Hemophilia Study included males with severe factor VIII deficiency (<2%) without inhibitors but excluded those with severe developmental disorder, significant psychiatric disorder, or insufficient fluency in English. Assessments included the Wechsler Individual Achievement Test (WIAT) and the Child Health Questionnaire (CHQ), a parent-reported measure of the child's quality-of-life, with a

focus on the physical health summary (CHQ-PhS) score (**Supplemental Table S1**). Most (62%) were on prophylaxis at enrollment or had been on prophylaxis previously (9%), providing a comparison between children of similar age, hemophilia severity, parental education, and IQ ever-treated with prophylaxis (2.7 months-7.7 years) and never-treated with prophylaxis. Overall achievement scores were within the average range, and those with 11 or fewer bleeds had better total achievement than those with 12 or more bleeds. The number of bleeding episodes was positively correlated with school absenteeism. Even after adjusting for the child's IQ and parents' education, children with more school absences had lower scores in mathematics, reading, and total achievement. Children with fewer bleeding episodes had better CHQ-PhS scores than children in the high bleeding episode category, and the mean CHQ-PhS score for children in the higher bleeding episode group was lower than the mean for the general US population. The authors concluded that allowing males with hemophilia to achieve their academic potential is an important medical outcome distinct from focus on musculoskeletal outcomes, and that in part, the adequacy of control of bleeding via the treatment plan may affect school performance.<sup>22</sup>

There were two cross-sectional studies published a few years apart that focused on comparisons of behavioral/emotional issues and social functioning against a control group. The Pediatric Hemophilia Clinic at St James's University Hospital (Leeds, UK) in 2000 explored emotional and behavioral problems in hemophilia and the impact on family functioning by examining families with and without children with hemophilia. The two groups were similar in age and the number of children in the family; however, fewer mothers in the hemophilia group worked outside of the home, and they were responsible for administering treatment injections in over half the cases. Across the Child Behavioral Checklist (CBCL) and Family Assessment

Measures (FAM) (**Supplemental Table S1**), more emotional, behavioral, and family difficulties were identified within the hemophilia group compared with the healthy school peers group but the difference did not achieve statistical significance due to the small sample size.<sup>21</sup> In the second study, three US treatment centers assessed social, emotional, and behavioral function children with hemophilia using a combination of assessments by teachers, classmates, parents, and the participants (**Supplemental Table S1**). In contrast to prior studies, no differences in social functioning were identified in comparison with a similar sized group of healthy peers matched on age and race; children with hemophilia were identified as popular, prosocial, disruptive, or sensitive by teachers, peers, and the children themselves at rates similar to comparable non-hemophilia peers. Social acceptance scores indicated that children with hemophilia were liked equally well by classmates and had similar numbers of best friends in the classroom. However, children with hemophilia reported more difficulty with emotional well-being, including more depressive symptomatology and lower self-perception; parents also reported more difficulties with emotional well-being. In addition, findings suggested that moderate-severe hemophilia was associated with increased depression, increased aggression/rejection, and less peer-rated aggression/disruption.<sup>23</sup>

### **Consequences of Intracranial Hemorrhage**

One possible covariate to cognitive and behavioral problems in children with hemophilia is the potential impact of head injury and ICH. Two more recent studies highlight the long-term consequences of ICH in children with hemophilia. The Great Ormond Street Hospital for Children NHS Trust database identified males with hemophilia and ICH and controls with hemophilia but no history of ICH. Assessments with the Strength and Difficulty Questionnaire (assessing emotion, conduct, behavior

and relationships) (**Supplemental Table S2**) found that children with hemophilia and ICH were more likely to have problems with motor function and visual-motor integration and a tendency towards problems compared to controls.<sup>26</sup>

Using a similar approach, the pediatric hemophilia clinic at Toronto's Hospital for Sick Children determined that males with hemophilia and ICH had lower intellectual functioning, visual-spatial skill, fine motor skill, vocabulary, reading skills, and math skills compared to males with hemophilia only. However, the study found no differences between the two groups on attention, socio-emotional functioning, behavioral problems, executive functioning, and adaptive functioning, most likely due to the small sample size. The authors concluded that "although ICH is not 'benign,' it was not associated with significant cognitive and academic consequences for most boys" in their small study.<sup>27</sup>

### **Need for Updated Assessment of Neurocognitive Function**

Despite advancement in recombinant factor replacement and widespread adoption of routine prophylaxis, particularly for children with severe hemophilia, no additional studies have been conducted in recent years to evaluate the impact of hemophilia on children across hemophilia severities (mild-moderate-severe). In addition to a reduction in joint-related comorbidities due to prophylaxis, rates of HIV and hepatitis C are currently negligible in patients with hemophilia younger than ~30 years due to the initiation of plasma donor screening for HIV (1985) then HCV (1990), improved viral inactivation methods, and the availability of recombinant factor replacement products (since 1992). Assessment of aspects of neurodevelopment—particularly around gross and fine motor performance by physical therapists and academic performance and behavior by nurses, social workers, and psychologists (in some

centers)—are actively explored during annual or semi-annual comprehensive visits to HTC; however, the focus is typically on documentation of the concerns that are present and not on screening for potential abnormalities or areas of concern that may need further attention.

Much as it is now appreciated that joint microbleeds visible on MRI occur in patients on routine prophylaxis and may contribute to joint deterioration over time even in the absence of overt clinical signs of bleeding,<sup>28,29</sup> conservative use of imaging studies in the context of concussions/head injury may be leading us to underestimate the occurrence of potential cognitive impact of brain microbleeds in the absence of obvious trauma or concussion.<sup>30</sup> This may occur in children with severe hemophilia on routine prophylaxis or children with mild or moderate hemophilia who are being treated only as needed for infrequent bleeding episodes, the latter being more likely perhaps to engage in activities that are not thought of as high-risk contact sports (e.g. bouncy house). Combined with psychological impact of living with a chronic disease, this could be a physical substrate for ongoing cognitive impact in children/young adults with hemophilia.

### **eTHINK Study**

The eTHINK study (NCT03660774) is a one-time, prospective, cross-sectional, comprehensive, study of males aged 1 to 21 years with hemophilia A and B across severities and treatment regimens. The objective of this non-interventional study is to develop a hemophilia normative dataset for neurologic, neurocognitive, and neurobehavioral function and development in children and young adults with hemophilia to identify whether children with hemophilia remain at risk for accrual of cognitive and behavioral problems at higher rates than the general US population.

Analysis of the data will identify predictors of poor performance/behavior that can be used to implement screening programs, and this data could be used to assess any patients exposed to treatments or treatment regimens with potential positive or negative impact on cognitive function and behavior.

Following ethics review and informed consent, data will be collected on approximately 510 males with hemophilia using a structured developmental and hemophilia history, a comprehensive neurologic examination, and age-appropriate assessments of neurodevelopment,<sup>31</sup> including assessment of intelligence,<sup>32,33</sup> emotional behavior,<sup>34</sup> adaptive behavior,<sup>35</sup> executive function,<sup>36,37,38</sup> and attention and processing speed with standardized and age-normed instruments.

In the HIV/HCV and pre-prophylaxis era, the HGDS and other studies demonstrated that hemophilia has an impact on the cognitive performance, behavior, and attention of affected males. Although treatment of children with hemophilia has shifted towards encouraging routine prophylaxis for those with severe and in some cases mild and moderate disease, increased participation in activities may mean that children with hemophilia continue to experience an impact of their disease. Of ~140 HTC, the CDC lists 9 that incorporate clinical psychologists or neuropsychologists in a comprehensive care team, but barriers to reimbursement for neuropsychological assessment may limit the ability to routinely refer children with hemophilia for testing, and to specifically evaluate those with prior ICH or head injury, poor school performance, and behavioral problems noted by parents and teachers. The cross-sectional eTHINK study will provide an updated assessment across the spectrum of hemophilia severity and potentially point to predictors of risk for children with hemophilia.



## **Conflict of Interest Statement**

C Buranahirun is a site PI of eTHINK study. K Walsh is a consultant for Novo Nordisk and a site PI of eTHINK study. C Mrakotsky is a consultant for Novo Nordisk, co-author of the eTHINK study protocol, site Co-PI of the eTHINK study and served as a speaker for Otsuka Pharmaceutical. SE Croteau is a site PI of eTHINK study, is a consultant for Bayer, CSL-Behring, Genentech, Novo Nordisk, Octapharma, Shire and has received research funding from Genentech, Pfizer, Spark Therapeutics, and ATHN/Hemophilia of Georgia Research. M Rajpurkar has received research grants from Pfizer Inc, Bristol Myers, Squibb, and Novo Nordisk (for clinical studies); and is a consultant with Novo Nordisk, Pfizer, Spark Therapeutics, Kedrion, Hema Biologics, and a Shire advisory board member. S Kearney has received grant/research support from Bayer, Bioverativ, Daiichi Sankyo, Grifols and Novo Nordisk and served on speaker/advisory boards for Bayer, Bioverativ and Novo Nordisk. C Hannemann has no conflict of interest. GN Wilkening has no conflict of interest. KA Shapiro has received fees as a consultant for Novo Nordisk. DL Cooper is an employee of Novo Nordisk (sponsor of eTHINK study).

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TABLE 1 Summary of HGDS and follow-up studies

Study/Citation	Design	Domains/Focus Areas	Key Findings
<b>Hemophilia Growth and Development Study</b>			
Hilgartner 1993, Bale 1993, Loveland 1994, Watkins 2000, Mitchell 1993, Wilson 1992, Nelson 2000, Sirois 1998, Loveland 2000, Nichols 2000, Usner 1998, Mitchell 1997, Bordeaux 2003	Males ages 6-18 years, n=333 with hemophilia, 14 US HTCs, Initial evaluation and 4-year follow-up	Baseline growth, neurologic, immunologic, neuropsychological functioning, neuroimaging	<ul style="list-style-type: none"> <li>• Baseline neurologic exam abnormalities common (e.g. gait, coordination, motor function)<sup>17</sup></li> <li>• 12 ICHs on baseline magnetic resonance imaging, frequent non-haemorrhagic and white matter lesions<sup>10,12</sup></li> <li>• Academic/adaptive skills lower than expected; more behavioral/emotional problems<sup>8</sup></li> <li>• Lower intelligence/achievement scores associated with more severe hemophilia<sup>16</sup></li> <li>• Attention abnormalities related to prior ICH (known or silent)<sup>9</sup></li> <li>• Caregiver-perceived psychosocial issues associated with immune compromise<sup>18</sup></li> </ul>
Mayes 1996	Males ages 5-17 years, n=66 with hemophilia, US HTC, cross-sectional study	ADHD/learning disabilities	Higher prevalence of ADHD (28%), learning disabilities (16%) <sup>19</sup>
Wodrich 2003	Males ages 5-14 years, n=34 with hemophilia, US HTC, cross-sectional study	Inattention/hyperactivity	ADHD is over-represented in the hemophilia population <sup>24</sup>
Spencer 2009	Males ages 6-12 years, n=19 with hemophilia, n=22 controls, US HTC, cross-sectional study	Inattention/hyperactivity and academic skills	<ul style="list-style-type: none"> <li>• Teacher ratings endorsed more problems with hyperactivity/inattention in CwH, while parents endorsed more hyperactivity only</li> <li>• CwH committed more</li> </ul>

			<ul style="list-style-type: none"> <li>impulsivity errors</li> <li>Trend towards lower math/reading performance, higher enrollment in special education<sup>25</sup></li> </ul>
Smith 1997	Males ages 6-18 years at study initiation, n=14 with hemophilia, n=13 with hemophilia and HIV, n=9 controls, Canadian HTC, Longitudinal 3-year study	Neuropsychological functioning	Lower than expected academic achievement in all groups <sup>20</sup>
<b>Academic Achievement Study</b>	Males ages 6-12 years, n=131 with hemophilia, US HTCs, cross-sectional study	Academic achievement	Irrespective of regimen, lower frequency of bleeding episodes correlated with better achievement <sup>22</sup>
Shapiro 2001			
Evans 2000	Males ages 4-15 years, n=24 families of males with hemophilia, n=12 controls, United Kingdom HTC, cross-sectional study	Emotional/behavioral functioning	More emotional, behavioral and family difficulties identified in CwH group <sup>21</sup>
Trzepacz 2003	Males ages 8-14 years, n=40 with hemophilia, n=40 control, US HTCs, cross-sectional study	Social/emotional/behavioral functioning	<ul style="list-style-type: none"> <li>Increased difficulty with emotional well-being and lower self-perception</li> <li>Moderate to severe CwH with increased depression, increased aggression/rejection, and less peer-rated aggression/disruption increased difficulty with emotional well-being and lower self-perceptions<sup>23</sup></li> </ul>
Bladen 2009	Males ages 4-12 years, n=6 with hemophilia and ICH, n=11 controls with hemophilia, United Kingdom HTC, cross-sectional study	Long-term consequences of ICH	<ul style="list-style-type: none"> <li>More likely to have problems with motor function, visual motor integration</li> <li>Tendency towards elevated problems on the Strength and Difficulty Questionnaire<sup>26</sup></li> </ul>
Miles 2012	Males ages 3-7 years, n=16 with hemophilia and ICH, n=16 with hemophilia, Canadian	Impact of ICH on cognition, academic performance,	<ul style="list-style-type: none"> <li>No differences between ICH and control on parent questionnaires</li> <li>Intellectual functioning lower</li> </ul>

HTC, cross-sectional  
study

behavior

in ICH group: visual-spatial  
skills, fine motor skills,  
vocabulary knowledge, word  
reading, math problem  
solving

- Higher than expected rate of  
learning disabilities (16%)<sup>27</sup>

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ADHD, attention deficit hyperactivity disorder; CwH, children with hemophilia; HTC, hemophilia treatment  
center; ICH, intracranial hemorrhage

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