Urological disorders are still the leading cause of inhospital death in patients with spina bifida

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Benoit PEYRONNET [1,2,3], Fei GAO [4], Charlène BROCHARD [2,3,5], Emmanuel OGER [6], Lucie-Marie SCAILTEUX [6], Frédéric BALUSSON [6], Juliette HASCOET [1,2,3], Quentin ALIMI [1,2], Zine-eddine KHENE [1], Sahar BAYAT [4], Magali JEZEQUEL [2], Camille OLIVARI [2], Caroline VOIRY [2,7], Jacques KERDRAON [2,8], Guillaume BOUGUEN [2,3,5], Xavier GAME [9], Laurent SIPROUDHIS [2,3,5], Andrea MANUNTA [1,2,3]

1: Service d'urologie, CHU Rennes, 35000 Rennes, France

2: Centre de référence spina bifida, CHU Rennes, 35000 Rennes, France

3: Equipe thématique INPHY CIC 1414 et INSERM UMR 1241, Rennes, France

4: EHESP Rennes, Sorbonne Paris Cité, Paris, France.

5 : Service de Gastro-Entérologie, CHU Rennes, 35000 Rennes, France

6 : Univ Rennes, CHU Rennes, REPERES (Recherche en Pharmaco-épidémiologie et Recours aux Soins) 35000 Rennes, France

7: Service de Médecine Physique et Réadaptation, CHU Rennes, 35000 Rennes, France

8: Centre de rééducation de Kerpape, 56270 Ploemeur, France

9: Département d'Urologie, Transplantation Rénale et Andrologie, CHU Rangueil, 33000 Toulouse, France

Corresponding author

Benoit Peyronnet

Service d'Urologie, Hopital Pontchaillou,

2 rue Henri Le Guilloux, 35000 Rennes, France

mail: peyronnetbenoit@hotmail.fr

Phone number: +33299284321

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Abstract

Objective

To assess and analyze the contemporary causes of inhospital deaths of spina bifida patients.

Methods

It was a cross-sectional observational study of the longitudinal national cohort of all patients hospitalized in French public and private hospitals. We analyzed the data from the French hospital discharge database (Programme de Médicalisation des Systemes d'Information, PMSI) from 2009 to 2014. The number of inhospital deaths was extracted using the combination of the ICD-10 codes "Q05" or "Q760" and a discharge code=9.

Results

There were 138 inhospital deaths of spina bifida patients over the 6-year study period. The median age at death was 41 years (IQR: 25-52). The median age at death was significantly lower in patients with vs. without hydrocephalus (26.6 vs. 45.5 years; p<0.0001). The leading cause of inhospital death was urological disorders (n=24; 17.3%). Other main causes of death were pulmonary disorders (n=23; 16.7%), neurological disorders (n=19; 13.8%) and bowel disorders (n=15; 10.9%). Upper urinary tract damage accounted for most of the urological causes of death: eight patients died from urinary tract infections (33.3%), seven patients died from renal failure (29.2%), four died from bladder cancer (16.7%) and five from other urological causes. The only variable significantly associated with a death from urological causes was the absence of hydrocephalus (OR=0.26; p=0.009).

Conclusion

Urological disorders remain the leading cause of inhospital death in spina bifida patients in France. The present study highlights that efforts to improve the urological management of the spina bifida population are still greatly needed.

Introduction

Spina bifida is a birth defect originally defined as an incomplete closure of the neural tube in the caudal region resulting in protrusion of part or all of the content of the spinal canal through this dorsal defect [1]. Spina bifida is the most common congenital cause of neurogenic bladder with an incidence of 1/10,000 births in developed countries [1-2]. Neurogenic lower urinary tract dysfunction (NLUTD) is present in more than 90% of spina bifida patients and carries a high-risk of upper urinary tract damage; namely pyelonephritis, urolithiasis and chronic kidney disease (CKD) [3]. Urological disorders in general, and upper urinary tract damage due to NLUTD in particular, have for long been reported as the leading cause of death in spina bifida patients [4-6]. However, most of the available data focused on the pediatric population and date back to over two decades [4-5]. Owing to improvement in healthcare and understanding of this condition, a larger proportion of spina bifida patients survive into adulthood nowadays [7]. The second reason why urological disorders might no longer be the predominant cause of death in spina bifida patients is the significant improvement of neurourological care over the past two decades. The primary aim of the present study was to assess and analyze the contemporary causes of inhospital deaths of spina bifida patients.

Methods

Study design

It was a cross-sectional observational study of the longitudinal national cohort of all patients hospitalized in French public and private hospitals. We analyzed the data from the French hospital discharge database (Programme de Médicalisation des Systemes d'Information, PMSI) from 2009 to 2014. The spina bifida patients were identified using the following International Classification of Diseases (ICD)-10 codes: Q05 ("spina bifida") or Q760 ("spina bifida occulta"; this code also including sacral agenesis). All the patients with these codes recorded as principal or secondary diagnoses were included with no age restriction, i.e. both children and adults were included as long as they were considered living birth (i.e. stillborn were excluded). The PMSI database is a comprehensive nationwide registry of all inpatient hospital stays collecting core informations about the patient's demographics and the stay (length, procedures, diagnoses) for billing purposes [8]. Each record is for a single hospitalization; thus, multiple records are possible for an individual with recurrent hospitalizations. To estimate the number of living spina bifida patients over the study period, duplicates were removed thanks to the unique patient identifier available in the PMSI

database, allowing to extract the total number of spina bifida people with at least one inhospital stay over the six years of the study period.

Deaths and their causes

The number of inhospital deaths was extracted using the combination of the aforementioned ICD-10 codes ("Q05" or "Q760") and a discharge code=9, which is the discharge code for death. In accordance with the French national regulations, due to the absence of direct involvement of patients and the retrospective nature of the study design, informed consent was not required [8].

The causes of death were obtained using the principal diagnosis recorded for the last RUM ("Résumé d'Unité Médical", i.e. summary of medical unit") of the hospital stay whose discharge code was 9. Those principal diagnoses are coded according to the ICD-10.

The causes of death were then analyzed by two independent reviewers and categorized as follows: urological, pulmonary, neurological, digestive, musculo-skeletal, cardiovascular, infectious, cancer, others. Any disagreements were resolved by discussion between the two reviewers or, if needed, by consulting a third person. The urological causes of death were then categorized as follows: urinary tract infections (ICD-10 codes: "N10", "N110", "N111", "N390", "N410"), renal failure (ICD-10 codes: "N132", "N133", "N178", "N179", "P960"), bladder cancer (ICD-10 codes: "C678", "C679") and other urological causes (ICD-10 codes: "N312", "N360", "N995", "Z466").

For each dead patient, age and gender were also extracted as well as the type of spinal dysraphism: open (ICD-10 code "Q05") vs. closed (ICD-10 code "Q76") and the coexistence or not of hydrocephalus and the neurological level (categorized as cervical/thoracic vs. lumbar/sacral vs. undetermined). All data generated or analyzed during this study are included in this published article and its supplementary information files.

Statistical analysis

Quantitative variables were expressed as median and interquartile range and categorical variables as numbers and proportions. Categorical variables were compared using the Chi-2 test and quantitative variables using the Mann-Whitney test. Univariate logistic regression analyzes were used to assess the variables associated with death from urological cause. For continuous variables, odd ratios were expressed as a range (per change in regressor over

entire range). Statistical analyses were performed using JMP v.12.0 software (SAS Institute Inc, Cary, NC, USA). The statistical significance level was set at $p< 0.05$.

Results

Study population

The number of spina bifida patients hospitalized at least once over the study period ranged from 1,562/year in 2009 to 1,739/year in 2014. Hence, after removal of all duplicates, the total number of living spina bifida patients over the study period was estimated to be 8,164.

The number of inhospital deaths of spina bifida patients per year fluctuated between 14/year in 2012 and 31/year in 2011 making a total of 138 inhospital deaths over the 6-year study period. The median age at death was 41 years (IQR: 25-52). There were 64 male patients (46.4%) and 74 female patients (53.6%). Most patients had open spinal dysraphism (n=131, 95%) and 54 had an hydrocephalus (39.1%). The neurological level was cervical/thoracic in 16 patients (11.6%), lumbar/sacral in 58 patients (42%) and undetermined in 64 patients (46.4%). The median age at death was significantly lower in patients with vs. without hydrocephalus (26.6 vs. 45.5 years; $p<0.0001$).

Causes of death

The distribution of the causes of death is displayed in figure 1. The leading cause of inhospital death was urological disorders (n=24; 17.3%). Other main causes of death were pulmonary disorders (n=23; 16.7%), neurological disorders (n=19; 13.8%) and bowel disorders (n=15; 10.9%). The details of all causes of death are presented in table 1. Upper urinary tract damage accounted for most of the urological causes of death: eight patients died from urinary tract infections (33.3%), seven patients died from renal failure (29.2%), four died from bladder cancer (16.7%) and five from other urological causes (respectively one from ostomy complication, one from urethral fistula, two from neurogenic bladder and from urinary retention).

Predictive factors of death from urological causes

The only variable significantly associated with a death from urological causes was the absence of hydrocephalus (OR=0.26; p=0.009; table 2). There was no association between

the gender (OR=0.79; p=0.61), the age at death (OR=1.92; p=0.51), the neurological level (OR=1.68; p=0.50) or the type of spinal dysraphism (OR=0.78; p=0.82) and a death from urological causes.

Discussion

To our knowledge, most studies on the causes of death of the spina bifida population date back to over two decades [4-6; 9]. Those former studies suggested that urological disorders were the predominant causes of death of spina bifida patients in the 1980s' and 1990s' [4-5]. One may have postulated that this situation would have changed in developed countries over the past twenty years with raising awareness of neurourological risks in the spina bifida population along with better understanding of spina bifida NLUTD [10-11] and significant advances in neurourology (e.g. intradetrusor botulinum toxin injections, anticholinergics, etc…) [12-13]. In the present study, we found that urological disorders remain the leading cause of death in the spina bifida population nowadays in a western country.

Of note, most urological deaths were due to upper urinary tract damage (i.e. urinary tract infections and renal failure) which results directly from NLUTD. Spina bifida NLUTD are characterized by high proportions of low bladder compliance and high detrusor leak point pressure [14] resulting in vesico-ureteral reflux favoring pyelonephritis, urolithiasis and ultimately end-stage renal failure [15]. Over the past decades, breakthroughs in neurourology such as the introduction of clean intermittent catheterization [16], anticholinergic medications [17] or intradetrusor injections of botulinum toxin [13] have contributed to dwindle the risk of severe urological complications in other neurologic populations [18]. Two main reasons might explain that these innovations did not translated into a reduced urological mortality in spina bifida patients. First, several studies have evidenced that spina bifida patients might be poorly responsive to some of these latest neurourological treatments, especially to intradetrusor botulinum toxin injections [19-20]. The other putative explanation could be the well-established difficulties of many spina bifida patients with medical adherence, heavily influenced by multifactorial issues such as cognitive dysfunctions, mental health issues and parenting behaviors [21-22].

One may wonder whether the national organization of spina bifida urological care and the functioning of the healthcare system might have impacted our findings. Reference networks are considered as key factors to deliver high quality care to patients with rare diseases [23]. In 2007, the French government set up a national plan for rare diseases with the aims to improve clinical management of these conditions within a multidisciplinary approach as well

as to promote clinical knowledge and research in this domain [24]. The spina bifida network was one of 130 networks for rare diseases created each with a single national expert centre coordinating the work of regional referral centres. The objective was to harmonize and bring the clinical expertise close to the patient rather than the patient having to travel to find the expert center. Owing to the existence of such a national plan and reference network for spina bifida in France over the study period, it is unlikely that our findings could be explained by a national structural flaw in healthcare of this patients' population. However, future studies from other countries with different health care systems and other policies regarding rare diseases are needed to confirm the external validity of our findings.

Interestingly spina bifida patients with hydrocephalus were less likely to die from urological causes. Two assumptions could be made to explain this finding. First it could be hypothesized that those patients may have more severe neurological impairment exposing them to higher likelihood of death from neurological or musculoskeletal cause [25]. The other hypothesis would be that those patients would have a closer medical follow-up owing to their more severe disability, allowing for a better urological management.

The present study has several limitations that should be acknowledged. First it does not account for out-hospital deaths. It is likely that a large proportion of deaths occurred outside of hospitals and the number of deaths is likely to be widely underestimated. As a result, we decided not to calculate the mortality rate that would have probably been highly biased. Another significant shortcoming of the present study is the lack of a control group which may have allowed to determine whether inhospital mortality of spina bifida patients is premature or not and the specifics of spina bifida causes of death compared to other populations. The use of an administrative database has strengths and weaknesses. On the one hand, the PMSI is the French hospital discharge database and has major financial implications, being used to determine financial resources of healthcare institutions. Thus, PMSI data are thoroughly monitored by providers and paying parties ensuring high quality data. In addition, the PMSI is a comprehensive database allowing to conduct a nationwide study. On the other hand, the PMSI has significant flaws. As any administrative database, it includes only core information for billing purposes lacking many clinical data. This prevented in the present study, for instance, to assess more thoroughly predictors of death from urological causes. The other significant drawback of the PMSI database is that, similarly to other administrative datasets, it is subject to coding errors and limited by the relative lack of precision of existing codes and terminologies. Multiple contributors to the cause of death may have factored in for some patients which our database and study design could not account for and this may have biased partly our findings. Finally, another limitation inherent to the database was that the cause of death was undetermined for 19 patients. If theses causes were known this might

have changed our conclusion that urologic disorders are the leading cause of in-hospital death.

Conclusion

Urological disorders remain the leading cause of inhospital death in spina bifida patients in France. Deaths from urological causes occur at an early age. Several hypotheses could be made to explain this finding including lack of awareness of urological disorders in spina bifida patients, poor compliance of this population with urological cares, resistance to usual neurourological treatments, lack of neurourological care providers or improvable organization of the healthcare system. Pending future studies from other countries, which are needed to confirm these findings, the present study highlights that efforts to improve the urological management of the spina bifida population are still greatly needed. Despite the predominant role of urological disorders in spina bifida mortality, the overall very diverse causes of death and early mortality underline the paramount importance of multidisciplinary management of this patients' population.

Figure legends

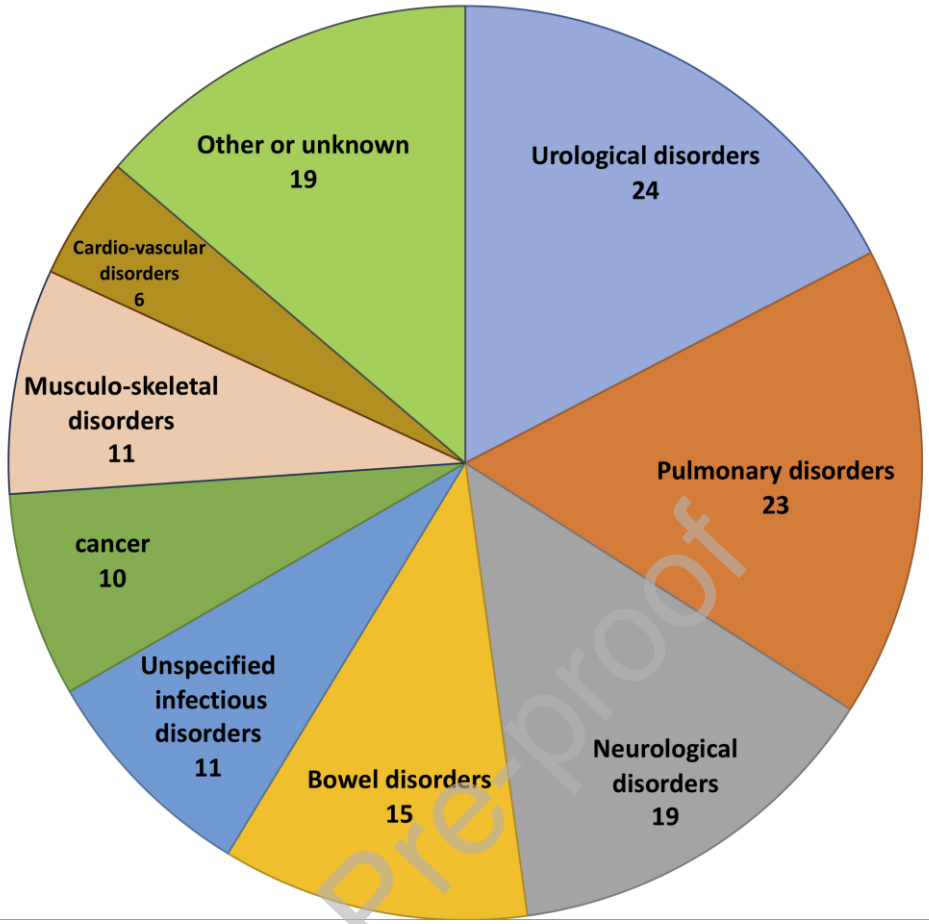

Figure 1: causes of inhospital deaths of spina bifida patients

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Table 1: Causes of inhospital death of the spina bifida population from 2009 to 2014

Causes of death	Number of patients N=138
Urological disorders	**24 (17.3%)**
Urinary tract infections	8
Renal failure	7
Bladder Cancer	4
Others	5
Pulmonary disorders	**23 (16.7%)**
Pneumonia	16
Acute respiratory failure	4
Bronchitis	2
Pulmonary embolism	1
Neurological disorders	**19 (13.8%)**
Hydrocephalus	5
Meningitis	4
Cerebrovascular accident	4
Seizures	3
Others	2
Bowel disorders	**15 (10.9%)**
Bowel obstruction	6
Peritonitis	3
Liver failure	2
Others	4
Musculoskeletal disorders	**11 (8%)**
Pressure ulcers	5
Cellulitis	2

Femoral Fracture	2
Scoliosis	1
Skin Cancer	1
Infectious disorders	**11 (8%)**
Septic shock of undetermined origin	11
Cancer	**10 (7.2%)**
Cancer of unspecified origin	10
Cardiovascular disorders	**6 (4.3%)**
Heart failure	5
Acute limb ischemia	1
Others/Undetermined	**19 (13.8%)**

Table 2: Univariate Logistic regression analyzes seeking predictors of death from urological causes

	Odds-ratio [CI-95%]	**p-value**
Age at death	1.92 [0.07-3.46]	0.51
Male gender	0.79 [0.32-1.92]	0.61
Hydrocephalus	0.26 [0.07-0.73]	0.009
Neurological level Lumbar/Sacral Cervical/thoracic	1.00 [Ref] 1.68 [0.33-7.01]	0.50
Closed spinal dysraphism	0.78 [0.20-24.72]	0.82