Spinal muscular atrophy (SMA) from the urological point of view: Assessment of the urinary function in 38 patients

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Abstract: Spinal muscular atrophy (SMA) includes genetic heterogeneous diseases characterized by muscle weakness and atrophy. There are at least two risk factors for SMA patients to develop urinary dysfunctions: 1) the neural degeneration, that influences the pelvic floor and sphincters; 2) the disabilities that predispose to constipation and urinary incontinence and symptoms. Nevertheless, the true incidence of urological disorders remains unknown. The evaluation of urinary symptoms in SMA patients remains scarcely investigated. The aim of our paper is to assess the association between urological disorders and SMA. We worked out a questionnaire to assess the voiding habits of patients with SMA followed at a single Italian Centre. We collected demographic data and information regarding respiratory, orthopedic and gastrointestinal involvement. We excluded patients <5 years of age. 38 patients were evaluated at a mean age of 12 years. Twenty-five patients had Type 2SMA, 13 Type 1 SMA. The respiratory system was involved in 35 patients, PEG was performed in 7 for failure to thrive and 26 suffered from constipation. Fifteen out of 38 (39%) patients wear diapers for urinary incontinence or...
for convenience. Two patients presented recurrent urinary retention requiring catheterization. No episodes of urinary infections nor urolithiasis were observed. Urinary function parameters were within the normal range. Our results suggest that the urinary function of SMA patients seems good. Nevertheless, a thorough urinary assessment in early childhood is important to identify bad habits in order to reduce the daily discomfort improving the quality of life.

**Subjects:** Medicine; Pediatric Nephrology; Pediatrics & Child Health

**Keywords:** SMA; urinary function; children; patients

1. Introduction

Spinal muscular atrophy (SMA) includes genetic disorders characterized by muscle weakness and atrophy related to degeneration of anterior horn cells in the spinal cord and brain stem nuclei (Prior & Finanger, 2000). The incidence of SMA is 1/6,000–11,000 live births (Darras, 2015). Considering pre and postnatal forms, there are five main phenotypes (Types 0, 1, 2, 3 and 4) with variable severity, age of onset and maximum motor function achieved. Each form is also characterized by different SMN2 gene copy number that correlates with clinical manifestations and prognosis. In particular, a low copy number (1 to 4 copies of SMN2) is associated with extreme weakness and paraplegia in neonates and infants and early need of respiratory support with the impossibility to sit or stand alone. A high copy number (4 to 8 copies of SMN2) is typical of adult forms with proximal limb weakness.

Patients are usually asymptomatic in early childhood (except for type 0), they progressively have a rapid functional loss and lately a static phase with slow progression. Rarely, there are periods of transient improvement after a progression (Darras, 2015; Prior & Finanger, 2000). Medial survival is different in the various phenotypes: weeks for type 0, <1 year for type 1, >25 years for type 2 and longer survival rates for types 3 and 4.

The standard testing for SMA is now the molecular evaluation after clinical suspicion (identification of hypotonic or “floppy” infants). Muscle biopsy, electrodiagnostic testing, MRI are usually unnecessary.

In recent years, innovations and advances in medical technologies have changed the standards of care of affected patients (Farrar et al., 2016; Moultrie et al., 2016). The understanding of the genetic and molecular basis of SMA has led to new pharmacologic or gene-based therapies to increase SMN2 expression (small molecule therapy, RNA-based therapy, gene therapy …) (Arnold et al., 2015).

Special attention has always been addressed to issues such as respiratory and nutritional cares, orthopaedic and rehabilitative supports, and emotional and social assistance (Arnold et al., 2015; Farrar et al., 2016; Garg, 2016; Moore et al., 2016; Moultrie et al., 2016). Preserving the respiratory function is a critical therapeutic goal, being a respiratory failure the main cause of death in SMA patients. The early implementation of non-invasive ventilatory support can improve quality of life and overall survival with possible improvement in chest wall compliance and lung development (Oskou et al., 2007). Cough stimulators, airway clearance and respiratory masks with positive pressures improve ventilator drive, reduce aspirations and mucus plugging (Panitch, 2009). Gastrointestinal issues are commonly observed in SMA children probably because of immobility, nutritional deficiencies and altered gastrointestinal mobility (Karasick et al., 1982). The first approaches include the thickening of liquids to reduce dysphagia and the introduction of a semisolid diet. When there are frequent aspirations, gastrointestinal reflux and severe delayed gastric emptying, we should consider gastrostomy placement and fundoplication to reduce pulmonary consequences of aspiration and maintain proper nutrition (Durkin et al., 2008).
Orthopaedic and rehabilitative supports aim at maintaining function, preventing deterioration and improving quality of life. Regular stretching has shown to preserve flexibility and to prevent contractures (Fujak et al., 2011).

On the other hand, the urological aspect is almost overlooked. Associated urinary symptoms have been only occasionally reported and, excluding an anecdotal report (Van Gool, 1997), there is just one publication that deals with the topic in a specific way (Van Gontard et al., 2001). The aim of our paper is to assess the presence of urological disorders in SMA patients by describing the voiding habits, the presence of infections and the rate and type of wetting.

2. Materials and methods
We collected information regarding patients affected by SMA and assisted at the Buzzi Children Hospital in Milan. The sample was of 38 patients. Data included age, sex, SMA Type, age at diagnosis, need for wheelchair assistance, bedridden, presence of gastrostomy or tracheostomy, need for respiratory support.

We reached our patients by phone contact and we used a questionnaire to investigate the urinary function. The assessment of urinary comorbidities was based on clinical evaluation, collection of medical history (UTI, urolithiasis …), laboratory tests (creatinine, electrolytes, blood urea nitrogen, Beta-2 microglobulin, urinalysis), and renal and bladder ultrasounds with an evaluation of post-voiding residual urine. Data were grouped and analysed with Microsoft® Office® Excel software. We limited our investigation to patients older than 5 years (≥5 years) in order to avoid urinary symptoms related to immaturity.

3. Results
We included in our study 38 patients, 21 males and 17 females with a mean age of 12 years (range 5–22). Survey’s results are listed in Table 1. Thirteen patients have Type 1 SMA (34%) and 25 (66%) had Type 2 SMA; the mean age at diagnosis was 4 months (range 2–24 months). Most of them use non-invasive respiratory support (30 patients, 79%) and 5 have a tracheostomy (13%). In seven cases (18%), we performed a PEG for poor weight gain and failure to thrive. Thirty-six patients (95%) are in wheelchair and two (5%) are bedridden. Urinary and faecal voiding control was reached between 2 and 3 years by 16 patients (42%), after 3 years by 14 (37%) and before 2 years of age by 2 (5%). In the remaining six cases (16%) the voiding control has never been achieved or at least parents cannot give a certain answer. Fifteen patients (39%) still wear a diaper for urinary incontinence or logistic problems (convenience of management): 6 of them have never removed it, 3 wear it only at night and 6 have put it again at a mean age of 13 years after a free period, mainly for convenience. Thirteen patients (34%) complained about incontinence. They describe their incontinence as the loss of small drops of urine during cough (stress urinary incontinence, n = 1) or prior to urination, especially when they wait too much for emptying the bladder (urge incontinence, n = 10). In two cases it was not possible to define the type of incontinence. Another reported urinary problem was urinary retention (n = 2, 5%). The two patients with recurrent episodes of urinary retention have Type 1 SMA and require occasional bladder emptying manoeuvres with urinary catheters. Constipation was found in 26 children (68%): two of them experienced soiling and 23 require enemas or oral stool softener. None of our patients experienced neither urinary tract infections nor urolithiasis. Blood pressure and blood test samples showed normal values in all patients.

4. Discussion
SMA is a congenital disorder inherited in an autosomal recessive manner. It is caused by a homozygous deletion of SMN1 gene (Prior & Finanger, 2000). The disorder includes heterogeneous entities that have in common the loss of motor function and thus muscular atrophy and a typical symmetrical, proximal predominant extremity weakness. SMN1 pathogenic variants are responsible for numerous SMA phenotypes that represent a broad spectrum without clear subtypes (Darras, 2015; Moultrie et al., 2016; Prior & Finanger, 2000). For this reason, the most used
Table 1. Survey’s results

38 SMA patients (21 males, 17 females)
Mean age = 12 years
Type 1 SMA (34%); Type 2 SMA (66%)

| Items considered          | Number of patients (%) | Considerations on the base of our experience and Literature review |
|---------------------------|------------------------|-------------------------------------------------------------------|
| **Respiratory system**    |                        |                                                                  |
|                           | 30 (79%) NIRS (non-invasive respiratory support) | • Extensively reviewed: progressive pulmonary dysfunction        |
|                           | 5 (13%) tracheostomy   | • Precise and defined management in terms of assessment;         |
|                           |                        | airway-secretion mobilization; airway-clearance; respiratory    |
|                           |                        | support                                                        |
| **Nutrition and hydration** |                        |                                                                  |
|                           | 7 (18%) PEG            | • Extensively reviewed                                           |
|                           |                        | • Active assessment is vital                                    |
|                           |                        | • Nasogastric feed in the majority of cases and gastrostomy     |
|                           |                        | (with or without fundoplication) in selected patients           |
| **Motor**                 |                        |                                                                  |
|                           | 36 (95%) wheelchair    | • Extensively reviewed: scoliosis for spine muscles weakness    |
|                           | 2 (5%) bedridden       | • Conservative management and surgery to improve QOL           |
| **Constipation**          |                        |                                                                  |
|                           | 26 (68%)               | The presence of faeces in the rectum alters the bladder         |
|                           | 23 enemas/oral stool   | emptying, favouring the onset of urinary problems               |
|                           | softener               |                                                                  |
|                           | 2 soiling              |                                                                  |
| **Toilet-training**       | < 2 y.a. = 2 (5%)      |                                                                  |
|                           | 2-3 y.a. = 16 (42%)    |                                                                  |
|                           | > 3 y.a. = 14 (37%)    |                                                                  |
|                           | Never = 6 (16%)        |                                                                  |
| **Urinary symptoms:**    |                        |                                                                  |
| Urinary incontinence     | 13 (34%)               | • Scarcely investigated                                         |
| Urinary retention        | 2 (5%)                 | • Difficult assessment                                          |
| UTI                      | None                   | • Association with constipation                                  |
| Uralithiasis             | None                   | • Possible fearsome consequences: negative effect on the        |
|                           |                        | emotional state, self-esteem and QOL                            |
| **Diaper**               | 15 (39%)               | • An help to overcome daily discomforts                         |
|                           | • 6/15 never removed   |                                                                 |
|                           | • 3/15 only at night   | •                                                                 |
|                           | • 6/15 reintroduced at 11-13 y.a. (convenience)                |                                                                 |

SMA = spinal muscular atrophy; NIRS = non-invasive respiratory support; PEG = percutaneous endoscopic gastrostomy; y.a. = years old; UTI = urinary tract infections; QOL = quality of life

classification is still the one based on the age of onset and motor function with prognostic and management implications. It includes three SMA types. In Type 1 SMA (Werdnig-Hoffman disease) there is a rapid loss of motor and respiratory function in the first year of life. Children are hypotonic, with poor head control and they never sit unassisted. The paradoxical breathing is due to weakness in intercostal muscles. There is the risk of failure to thrive and aspiration when the weakness extends to the tongue and pharyngeal muscles. Type 2 SMA includes children who sit independently but they do not walk. It is the intermediate form of SMA in terms of severity: many of the comorbidities are related to orthopaedic problems (scoliosis, joint contractures ...). In
Type 3 SMA (Kugelberg-Welander disease) the disease is mild, often with neither orthopaedic complications nor reduction of life expectancy.

Type 0 and 4 refer, respectively, to the prenatal onset (death within weeks) and to the adult form.

The clinical phenotype, the natural history and the innovative treatment options of patients with SMA have been extensively reviewed but the evaluation of associated urinary symptoms was considered in just one paper (excluding an anecdotal publication) (Van Gool, 1997; Von Gontard et al., 2001).

The incidence of incontinence among SMA patients is difficult to assess. The presence of smooth cells in the detrusor prevents the direct involvement of the bladder muscle, as previously reported (Von Gontard et al., 2001). However, the pelvic floor muscles and the external urethral sphincter are made of voluntary striated muscles and they could be part of the degenerative process.

Moreover, children with disabilities are at risk of developing all types of incontinence. During the growth of the child the incontinence has a higher likelihood of becoming a chronic condition and persisting into adulthood (Joinson, 2016; Von Gontard et al., 2016). To confirm this, it has been shown that patients with “special needs” have physical limitations (e.g., walking incapability, scoliosis, lying position) that act as contributing factors for constipation (Issenman et al., 1999). The presence of solid stool was a common finding also in our series. Indeed, constipation was reported in 68% of patients. It is interesting the fact that all patients complaining about urinary incontinence were constipated as well. As previously suggested, the presence of faeces in the rectum alters the bladder emptying, favouring the onset of urinary problems. A fearsome consequence is a negative effect that incontinence might have on the emotional state, self-esteem and quality of life of the child. We recorded 39% of patients that require diapers and most of them coexist peacefully with their condition (the diaper helps the child to overcome daily discomforts while in school). However, it is to say that 10 out of 15 patients with a diaper in our series have always used protections or have decided themselves to use them for convenience and not for a real need against incontinence. It would be different if a child, who has always been dry, starts losing urine or stools.

An interesting aspect is that when parents were asked if their child has never experienced “urinary problems”, the answer was no in all except 2 cases (5%). In contrast, when more specific questions were asked, it came out that the problem existed in 42% of patients (e.g., they reported urinary incontinence and retention). A possible explanation for this discrepancy is that wearing a diaper is considered as a means of convenience more than the expression of a problem of incontinence or a normal situation when the child has always used it. In addition, urinary symptoms are just a little expression of the underlying disease. In fact, the wetting is not a major concern considering the severity of concomitant problems. Another element that emerged from our survey is that growing up, children with SMA tend to retain urine, especially when they are at school. They frequently report that they do not want the aid of an “outsider” and they prefer waiting to be at home with their usual caregiver. This may partly explain the mean age at which the diaper was used again (13 years). Our results suggest that patients with SMA might have severe urinary co-morbidities (even if we do record neither urinary infections nor urolithiasis we had two children with urinary retention requiring catheterization). We have enlightened “bad urinary habits” that may persist and predispose to problems into adulthood.

5. Conclusions
The SMA patient is complex and faces daily challenges. Efforts are made in order to improve the life of patients, given the survival elongation. Unlike what happens in children with other disabilities, the urinary function is preserved in SMA. However, a detailed assessment of urinary habits is
important because it permits to identify patients at risk of developing urinary problems, to treat them effectively and to reduce the related daily discomfort.

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