A CONTEMPORARY ANALYSIS OF THE AUSTRALIAN CLINICAL AND GENETIC LANDSCAPE OF SPINAL MUSCULAR ATROPHY: A REGISTRY BASED STUDY

SUPPLEMENTARY MATERIAL

Table of contents

SUPPLEMENTARY TABLE S1. VARIABLES ANALYSED AND EXCLUDED IN THE STUDY

Variables analysed		**Variables excluded (missing data or non-contributory to the research question)**
Variable	**Data available (%)**	
Age	100	
Sex	100	Other *SMN1* variants
Diagnosis through screening or other	100	Genetic test method for *SMN1*
SMN1 variant	100	Genetic test method for *SMN2*
SMN2 copy number	54·3	Is variant c.859G>C present in *SMN2* gene?
Other family members with SMA	100	*SMN2* variant c.859G>C testing method
SMA type	100	Other genetic test information
Scoliosis	100	Gestational age at birth
Scoliosis surgery	100	Symptom onset period
Scoliosis surgery technique	100	Age at symptom onset
Date of surgery	100	Date of last exam for growth parameters
Developmental milestones (head control, rolling to side, sitting unassisted, standing with and without assistance, walking with assistance, walking unassisted, walking 10 m without assistance, climbing stairs	100	Height/ length
Loss of milestones – all the above		Method of height measurement
Wheelchair/mobility device use	100	Other method of height measurement, specify
Gastric or nasal tube fed?	100	Weight (kg)
Invasive ventilation	100	Head circumference (cm)
Non-invasive ventilation	100	Contractures (shoulders, elbows, wrists, fingers, hips, knees, ankles, jaw)
Disease-modifying therapy for SMA used? zolgensma, spinraza, evrysdi	100	Cobb angle
Date of treatment for Zolgensma (MM-YYYY)	100	Age in years when milestones gained
Weight at start of Zolgensma treatment (kg)	100	Who observed first the milestone
Duration of systemic corticosteroid administration (for zolgensma)	100	Useful function of hands
Spinraza used? And still taking spinraza?	100	Reaching overhead in sitting position

Date of spinraza start (MM-YYYY) and end, if so	100	Raising hands to mouth in a sitting position
Weight at start of Spinraza treatment (kg)	100	Wheelchair/mobility device use (choice=Currently, Part-time)
Spinraza reason for stopping	100	Wheelchair/mobility device use (choice=No (currently UNDER 2 years of age))
Small molecule drug used? And still taking?	100	Wheelchair/mobility device use (choice=Previously, Part-time (specify age started & stopped))
Date of risdiplam start (MM-YYYY)	100	Wheelchair/mobility device use (choice=Previously, Full-time (specify age started & stopped))
Weight at risdiplam start (kg)	100	Age started CURRENT Full-Time wheelchair use in years and months
Clinicians seen in the last 6 months (neurologist)	100	
Multidisciplinary clinic visit in the last 6 months	100	Gastric or nasal tube fed, currently or previously exclusively
Physiotherapist seen in the last 6 months	100	Gastric or nasal tube fed, currently or previously supplemented
General practitioner seen in the last 6 months	100	Volume of previous exclusive nutrition in millilitre (mL)
Rehabilitation specialist seen in the last 6 months (occupational therapist, speech therapist, dietician, orthotist, hydrotherapist, chiropractor)	82	Frequency of previous exclusive nutrition
Specify other therapist seen in the last 6 months (gynaecologist, endocrinologist, psychologist, urologist, etc)	82	Caloric intake of previous exclusive nutrition in kilojoules (kJ)
Were rehabilitative interventions undertaken in the last 12 months or since last update? Stretches, respiratory physiotherapy program, massages, home program, hydrotherapy, occupational therapy sessions, braces/ orthotics	100	Previously supplementary tube fed, start date (MM-YYYY)
Number of elective hospital admissions in the last 12 months or since last registry update	86·6	Previously supplementary tube fed, stop date (MM-YYYY)
PGI-S (Patient/Parent Global Impression of Severity) - How affected are you/your child now by SMA? and date	91·1	Volume of previous supplementary nutrition in millilitre (mL)
PGI-I (Patient/Parent Global Impression of Improvement) - How do you feel you/your child's condition has changed in last 6 months? and date	91·1	Frequency of previous supplementary nutrition
		Caloric intake of previous supplementary nutrition in kilojoules (kJ)
		Current exclusive tube feeding, start date (MM-YYYY)
		Volume of current exclusive nutrition in millilitre (mL)
		Frequency of current exclusive nutrition
		Caloric intake of current exclusive nutrition in kilojoules (kJ)
		Current supplementary tube feeding, start date (MM-YYYY)
		Volume of current supplementary nutrition in millilitre (mL)
		Volume of current supplementary nutrition in millilitre (mL)
		Caloric intake of current supplementary nutrition in kilojoules (kJ)
		Frequency of invasive ventilation previously

		Frequency of invasive ventilation currently
		Date started invasive ventilation previously (MM-YYYY)
		Date stopped invasive ventilation previously (MM-YYYY)
		Date started invasive ventilation currently (MM-YYYY)
		Assistance in airway clearance and/or secretion mobilisation, specify type & frequency of use
		Suction used? & Frequency of use?
		Chest percussion used? & Frequency of use?
		IPPV (intermittent positive-pressure ventilation) used? & Frequency of use?
		Cough Assist device used? & Frequency of use?
		IPPV (intermittent positive-pressure ventilation) used? & Frequency of use?
		Other pulmonary assistance used? & Frequency of use? Please specify
		Specify other type of pulmonary assistance
		Forced Vital Capacity (FVC) testing
		FVC date of test (MM-YYYY)
		FVC litre (L)
		FVC predicted percentage (%)
		Peak Cough Flow (PCF) testing
		PCF date of test (MM-YYYY)
		Zolgensma dosage given
		Zolgensma route of administration
		Name of corticosteroid (for Zolgensma treatment)
		Date of anti-AAV9 antibody test (for Zolgensma treatment) (MM-YYYY)
		Number of days anti-AAV9 antibody test performed before Zolgensma treatment
		Anti-AAV9 antibody test result (for Zolgensma treatment)
		Spinraza dosage given
		Spinraza frequency of dosage (every x day(s)/month(s)/years(s))
		Spinraza route of administration
		Spinraza following recommended dosing schedule
		Spinraza reason not following dosing schedule
		Risdiplam dosage given
		Risdiplam frequency of dosage (every x day(s)/month(s)/years(s))
		Risdiplam route of administration
		Risdiplam following recommended dosing schedule
		Allopathic drugs prescribed in the last 12 months (or since last registry update if that is less than 12 months ago), specify
		Vitamin D (bone health) and start date
		Calcium (bone health) and start date
		Bisphosphonate (bone health) and start date as above
		Drugs for gastroesophageal reflux
		Drugs for constipation
		Antibiotics (for respiratory health)
		Anticholinergic (for respiratory health)
		Influenza immunisation (yes=ongoing)
		Pneumococcal immunisation (yes=ongoing)

		Creatine (supplement)
		Acetyl-L-carnitine (supplement)
		Phenylbutyrate (supplement)
		Gabapentin (supplement)
		Thyrotropin-releasing hormone (supplement)
		Hydroxyurea (supplement)
		Valproate
		Albuterol/Salbutamol
		Other allopathic drug 1-3, specify
		Hospitalised or presented to emergency in the last 12 months or since last registry update if that is less than 12 months ago, specify details planned visits then acute/emergency
		Planned hospital admissions in the past 12 months, reason(s) for admission, number of days of stay, 1 - 10
		Number of acute hospital visits (including if presented at ER but not admitted) in the last 12 months or since last registry update if that is less than 12 months ago
		Acute 1 – 10; presented to emergency/ admitted; reason for visit, number of nights in hospital
		In addition to hospitalisations already reported, has the patient been diagnosed with any other comorbidities in the last 12 months or since last registry update if that is less than 12 months ago, specify
		Number of additional comorbidities (1 to 6) – COVID 19, cardiac diagnoses, etc,. Start and end dates, ongoing?
		Participation in clinical drug trials
		Was a validated motor measure taken in the last 12 months or since last registry update if that is less than 12 months ago
		Why wasn't a validated motor measure taken
		Specify injury / acute injury / illness that meant that validated motor measure was not taken
		CHOP-INTEND, date, score
		HFMSE (Hammersmith Functional Motor Scale Expanded), date, score as above
		RHS (Revised Hammersmith Scale)
		HINE Section 2
		WHO Motor Milestones
		9HPT (9-Hole Peg Test) – R & L hand
		BBT (Box & Blocks Test) – R & L hand
		RULM (Revised Upper Limb Module)
		Brooke (Brooke Scale of upper extremity function)
		Revised Brooke
		MFM (Motor Function Measure)
		6MWT (Six-Minute Walk Test)
		10MWT (Ten-Metre Walk Test)
		TUG (Timed Up & Go Test)
		EK2 (Egen Klassification)
		CHOP-ATEND
		Other validated measure 1-4, (specify)
		Dominant hand
		CGI-S (Clinician Global Impression of Severity) and date

		CGI-I (Clinician Global Impression of Improvement) - How does clinician feel you/your child's condition has changed in last 6 months? and date
		Zarit Burden Interview (ZBI), score, date (MM-YYYY)
		Other validated PRO taken
		PedsQL 3.0 (neuromuscular module), scores and dates
		PEDI-CAT
		SMA FRS
		ACEND
		ACTIVLIM
		DISABKIDS
		FSS
		Other validated PRO, specify
		CMAP (Compound Muscle Action Potential) scan
		DEXA (Dual Energy X-ray Absorptiometry) scan
		Muscle imaging

SUPPLEMENTARY TABLE S2: CHARACTERISTICS OF DECEASED INDIVIDUALS IN THE ANMDR

SMA phenotype	**Functional status**	**Age at death (years)**	**Year of death***	**Sex**	***SMN1* pathogenic variant**	**Number of *SMN2* copies**	**Clinical sequelae of weakness**	**SMN-augmenting therapy**	**Other clinical characteristics**
Type 0	Non-sitter	0·2	2021	Female	Compound heterozygous deletion and pathogenic sequence variant	1	Invasive ventilation 24 hours/day Exclusive nasogastric feeding	No	Preterm birth (34 weeks); prenatal onset of symptoms
Type 1	Non-sitter	0·4	2022	Male	Compound heterozygous deletion and pathogenic sequence variant	2	Exclusive nasogastric feeding from age 1 month	No	Palliative care from age 3 months
Type 1	Non-sitter	1·0	2020	Female	Homozygous pathogenic sequence variants	2	Non-invasive ventilation – not used Exclusive nasogastric feeding from age 7 months	No	Palliative care from age 5 months
Type 1	Non-sitter	9·2	2021	Male	Homozygous deletion of exon 7	3	Non-invasive ventilation & feeding support – not used Scoliosis, requiring surgery (growing rods) at age 8 years	Commenced at age 6 years	
Type 2	Non-sitter	11·9	2022	Male	Homozygous deletion of exon 7	Not known	Non-invasive ventilation <16 hours/day from age 6 years Feeding support – not used Scoliosis, requiring surgery (arthrodesis) at age 9·5years	No	

*SMN-augmenting therapies were available during this period in Australia

SUPPLEMENTARY TABLE S3: MULITPLE IMPUTATION DATA - IMPUTED P-VALUE DESCRIPTIVES

1. Association between SMA type and *SMN2* copy numbers	
1.1 Homozygous deletion of exon 7 of *SMN1*: Significant relationship between *SMN2* copy number and SMA type (p<0.0001, Fisher's exact test); all imputed values <0·0001	
Minimum	$6{\cdot}1 \times 10^{-24}$
Median	$2{\cdot}2 \times 10^{-20}$
Maximum	$9{\cdot}8 \times 10^{-18}$
1.2 Compound heterozygosity/ biallelic sequence variants in *SMN1*: No significant relationship between *SMN2* copy numbers and SMA type (p=0·21, Fisher's exact test); imputed mean p=0·1282424; all imputed p-values >0·05	
Minimum	0·055
Median	0·055
Maximum	0·21
2. Clinical outcomes	
2.1 PGI-S*: No significant association between PGI-s and utilisation of therapies (p=0·792, Fisher's exact test); imputed mean p=0·7452292; all imputed p-values >0·05	
Minimum	0·62
Median	0·75
Maximum	0·86

2.2 PGI-I#: Significant relationship between PGI-I and utilisation of therapies ($p<0{\cdot}0001$, Fisher's exact test); all imputed p-values $<0{\cdot}05$	
Minimum	$4{\cdot}86 \times 10^{-9}$
Median	$3{\cdot}10 \times 10^{-8}$
Maximum	$8{\cdot}25 \times 10^{-8}$

*PGI-S: Patient/parent Global Impression of Severity

#PGI-I: Patient/parent Global Impression of Improvement