PRECOCIOUS PUBARCHE IN SMA PATIENTS WITH SEVERE SARCOPENIA

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CONTEXT

Spinal muscular atrophy (SMA) is an autosomal recessive inherited disease characterized by degeneration of anterior horn cells of the spinal cord and brainstem resulting in variable degrees of muscular atrophy and proximal muscle weakness. In December 2016, nusinersen was FDA-approved for the treatment of SMA in pediatric and adult patients. The introduction of this therapeutic modality has provided a platform for professional medical-care providers in our national neuromuscular center. To the best of our knowledge, this is the first report on endocrine manifestations in patients with severe forms of SMA.

AIMS

- To identify endocrine characteristics of SMA patients with precocious pubarche

STUDY DESIGN, PATIENTS & METHODS

Design: Real-life data were collected during routine clinic visits prior to nusinersen intervention

Patients: 62 SMA patients (24 type 1, 21 type 2, 17 type 3)

Outcome measures:

- Prevalence of SMA patients with precocious pubarche
- Weight status:
  - BMI SDS (≥ 3 years)
  - weight/ length SDS (< 3 years)

Laboratory evaluation:

- **Basal androgen profile levels** (testosterone, 17-hydroxyprogesterone, androstenedione and dehydroepiandrosterone sulfate)
- **Synacthen stimulation testing** for the diagnosis of adrenal enzymatic disorders (as clinically indicated)
- Homeostatic Model Assessment of Insulin Resistance [**HOMA-IR**] = fasting glucose (mg/dL)X fasting insulin/ 405

RESULTS

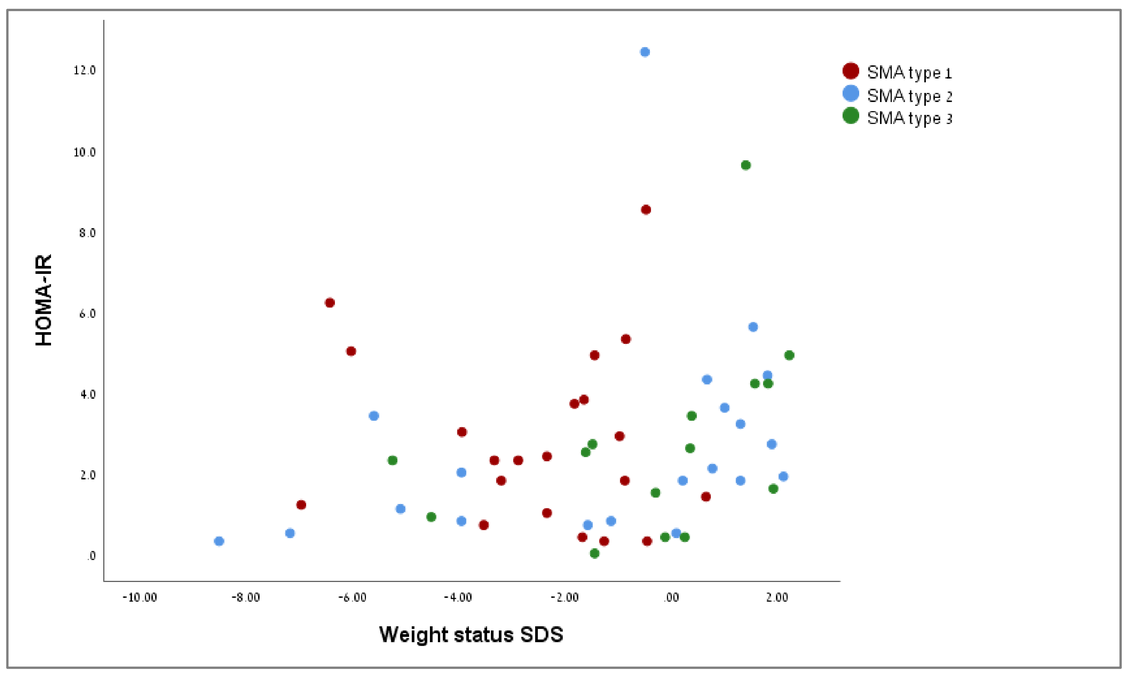
- **Precocious pubarche**: 15 out of 62 (24.2%) of the SMA cohort
- One SMA type 2 patient with rapid progression of adrenarche was diagnosed with non-classic congenital adrenal hyperplasia by Cosyntropin stimulation test (peak 17-OHP levels 72 ng/ml with normal cortisol reserve) and was excluded from analysis.
- 14 patients with precocious pubarche (mean age at onset 3.9 ± 2.8 years), without rapid progression had no other clinical signs or laboratory evidence of hyperandrogenism.

SMA patients with and without evidence of precocious pubarche

	Precocious Pubarche	No evidence of precocious pubarche	*P*
Number (percent)	15 (24.2)	47 (75.8)	
Sex, males	5 (33.3)	22 (46.8)	.359
SMA type 1	11 (73.3)	13 (27.7)	.002
SMA type 2	4 (26.7)	17 (36.2)	
SMA type 3	0 (0)	17 (36.2)	
HOMA-IR, mean (SD)	4.1 (2.9)	2.4 (2.0)	.017
Creatinine, mean (SD)	0.09 (0.04)	0.20 (0.12)	.001
Weight status-SDS, mean (SD)	-2.09 (2.91)	-1.39 (3.19)	.285

Data are presented as number (percent) unless otherwise specified. Chi-Squared or Fisher's exact test were applied for categorical variables and the Mann-Whitney test for quantitative or ordered variables.

HOMA-IR and weight status in patients with SMA



Scatter plot of insulin resistance (HOMA-IR) and weight status.

- Weight status of the study cohort was relatively low (-1.34 ± 2.65) with no significant differences between groups.
- SMA patients with precocious pubarche were characterized by significantly higher HOMA-IR levels and significantly lower creatinine levels compared to those without precocious pubarche.
- The association between insulin resistance and weight status displayed a bimodal distribution, with increased insulin resistance in the severely underweight patients and in patients with obesity.

CONCLUSIONS

Our findings suggest that isolated precocious pubarche is a common clinical manifestation in the severe types of SMA with markedly decreased muscle mass. Isolated precocious pubarche in those patients is characterized by increased insulin resistance without laboratory evidence of hyperandrogenism.

Further studies are warranted to delineate the role of sarcopenia and body fat/muscle imbalance in extreme underweight patients with precocious pubarche.