SUPPLEMENTARY TABLE. Complications, management, and follow-up of congenital central hypoventilation syndrome and associated complications

Problem	Presentation	Diagnosis and assessment	Management
Respiratory aspect			
Alveolar hypoventilation	Hypoventilation with SpO_2 <95% or $TcCO_2$ >45 mmHg (target: 35-45 mm Hg) Apnoea and desaturation	Patient awake: SpO_2, $TcCO_2$ or $ETCO_2$ Patient sleeping: polysomnography or C-reactive protein with SpO_2, $TcCO_2$, or $ETCO_2$ Assessment frequency: <2 years old: every 2-6 months ≥2 years old: annually More frequent if symptomatic	1. Non-invasive ventilation: nasal or oronasal masks, nasal prongs, and total face mask 2. Tracheostomy with positive pressure ventilation 3. Phrenic nerve pacing
Autonomic dysregulation of respiration	Lack of normal ventilatory and arousal responses to hypercarbia/ hypoxemia Limited breath-to-breath variability		
Cardiovascular aspect			
Cardiac arrhythmias	Sinus pauses and sinus bradycardia Decrease in HR variability Decrease in HR response to exercise and vasovagal syncope Prolonged R-R interval (risk of sudden death)	1. 48- to 72-hour ambulatory electrocardiogram 2. 24-hour ambulatory BP 3. Echocardiogram 4. Exercise/treadmill test for patients aged >6 years Annual review (more frequent if symptomatic)	1. Consider cardiac pacing for severe symptoms (use criteria from ACC/AHA guidelines for pacemaker implantation) 2. Consult paediatric cardiologist for pacing guidance in asymptomatic patients with R-R interval ≥3 seconds
Cardiovascular complications from autonomic dysfunction	Postural hypotension Nocturnal increase in BP and arterial hypotension during daytime		
Gastrointestinal aspect			
Hirschsprung disease	Failure to pass meconium within 24 hours after birth Abdominal distension and vomiting Constipation	1. Rectal suction biopsy: submucosal ganglion cell absence and increased acetylcholinesterase activity (gold standard) 2. Contrast study (least sensitive) 3. Anorectal manometry: absence of anal inhibition reflex in Hirschsprung disease Assessment frequency: individualised according to patient's condition	Surgical removal of affected intestine
Oesophageal dysmotility	Dysphagia and vomiting GERD	1. Upper GI contrast studies 2. Oesophageal manometry 3. Upper GI endoscopy: evidence of GERD 4. pH studies	1. GERD: H2 receptor antagonist or proton pump inhibitor 2. Antireflux surgery for chronic GERD
Ophthalmological aspect			
Pupillary defects	Abnormal pupillary dilatation and poor light response Anisocoria Severe miosis (more common) or mydriasis	1. Full examination by ophthalmologist 2. Visual acuity assessment 3. Neurological examination (cranial nerves) Annual review	1. Refraction errors: corrective lenses 2. Strabismus/ptosis: possible surgical correction Early detection and correction are important
Extrinsic oculomotor anomalies	Convergence insufficiency (exophoria and esophoria) Strabismus Third nerve palsy Isolated ptosis		
Ocular globe disorders	Abnormal iris: smooth iris and absence of crypts Microphthalmia		

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; BP = blood pressure; $ETCO_2$ = end-tidal carbon dioxide; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HR = heart rate; NPARM = non–polyalanine repeat mutation; PARM = polyalanine repeat mutation; SpO_2 = oxygen saturation; $TcCO_2$ = transcutaneous carbon dioxide

SUPPLEMENTARY TABLE. (cont'd)

Problem	Presentation	Diagnosis and assessment	Management
Neurological/neurodevelopmental aspect			
Acute complications	Breath-holding spells Seizures (related to arrythmias/ hypoxia) Syncope (25% of patients, mostly related to cardiac autonomic dysregulation)	1. Electroencephalogram and neuroimaging as appropriate 2. Workup for cardiac causes of seizure/syncope	Manage underlying cause
Long-term neurodevelopmental complications	1. Intellectual function impairment 2. Impairment in visual-perceptive skills, attention, language, memory, learning, and school performance 3. Below average visual/auditory memory skills	1. Early psychomotor developmental assessment 2. Neurodevelopmental follow-up Assessment frequency: <2-3 years old: every 4-6 months >6 years old: every 2 years As necessary if abnormality detected	1. Early and intensive intervention and training 2. Special education as appropriate 3. Respiratory management to avoid hypoxia
Social	Difficulties with social interactions Poor communication and daily living skills	Psychological assessment	Psychological support and counselling for patient and family
Endocrine aspect			
Autonomic dysregulation	Abnormal glycaemic control: Hypoglycaemia with hyperinsulinaemia Hyperglycaemia Growth hormone deficiency Hyperthyroidism	24-hour glucose monitoring Oral glucose tolerance test Growth monitoring Thyroid function monitoring	Treatment according to condition
Tumours aspect			
Neural crest tumours (recommended for PARM genotypes 20/28-20/33 and NPARMs)	Neuroblastomas Ganglioblastomas Ganglioneuromas	Clinical examination Chest X-ray and abdominal ultrasound Screening frequency: <2 years old: every 6 months 2-7 years old: every 6-12 months >7 years old: according to local protocol Consider magnetic resonance imaging (total body) and metaiodobenzylguanidine if indicated	Treatment according to tumour findings and local protocol

