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Jarcho-Levin syndrome – an imprecise clock

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This baby girl was born to a 28 year old GI/PI after an uneventful pregnancy by cesarean section at 40 5/7 weeks of gestation. The Apgar scores were 8, 9, 9 at 1, 5 and 10 minutes, respectively. Birth weight was 3.4 kg (P 25-50), birth length was 42 cm (<< P 3) and the head circumference was 35.5 cm (P 50-75). A marked deformation of the thoracic spine was noted and the child was transferred to our institution.

Clinical examination revealed a short and asymmetric thorax with a lordotic lumbar spine and a prominent gibbus formation of the thoracic spine. A wide nasal bridge was also present. The neurological exam was normal. X-ray showed a severe deformation of the cervical and thoracic spine and bilateral fusion of the ribs at the costovertebral angles (Fig. 1). The diagnosis of spondylothoracic dysplasia (STD) was made. Ultrasound examinations of the brain and the abdomen were otherwise normal. Echocardiography demonstrated a structurally normal heart and moderate pulmonary hypertension.

The initial course was uneventful and the girl was discharged home at the age of 10 days. She was regularly followed as an outpatient. She had to be hospitalized twice due to a viral respiratory infection and transient oxygen requirement. When she was 4 months old, her head circumference was 43.5 cm (P 90). Her family then spent the next three months abroad.

She presented again at our institution at the age of seven months due to failure to thrive. The examination revealed a head circumference of 53 cm, markedly above the 97th percentile. The anterior fontanel was tense and a cerebral ultrasound examination showed massive dilatation of all four ventricles. A ventriculoperitoneal shunt was put in place. An MRI of the CNS including the spine showed no stenosis of the spinal canal but the hydrocephalus was confirmed (Fig. 2). The etiology of the hydrocephalus therefore remained unclear. In the literature, there is no description of an association of spondylothoracic dysplasia and hydrocephalus.

At the time of this writing, the girl is 18 months old. Her most recent neurological examination showed reduced strength in both arms and atrophy of the muscles of the hands. The Griffiths developmental scales revealed a disharmonic profile: the personal-social, language and performance subscales were according to age, while there was a significant delay in the locomotor as well as in the eye and hand coordination part. The cause of the abnormal neurologic exam remains unclear but seems temporally related to the development of the subacute hydrocephalus. Orthopedic surgery of the spine is planned in the near future. For this purpose a CT scan of the thorax with 3D reconstruction was obtained (Fig. 3 and movie).

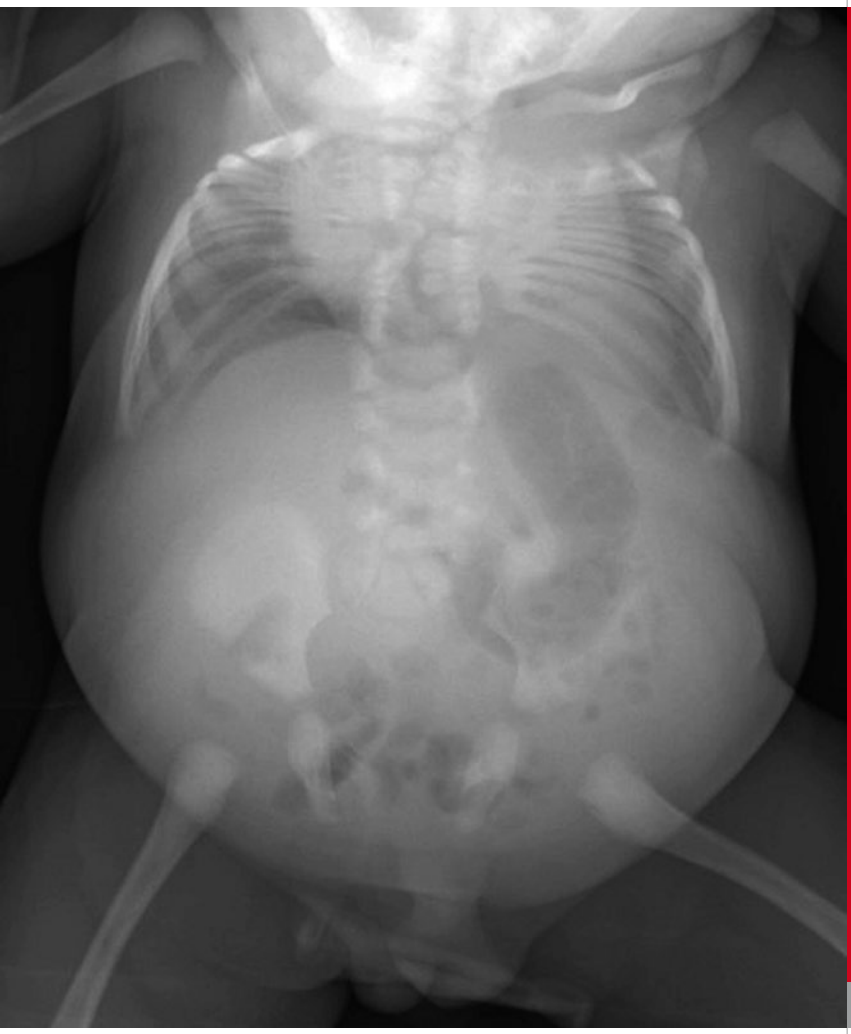

Fig. 1

Babygramm: "Crab-like" configuration of the ribs is typically seen in spondylothoracic dysplasia.

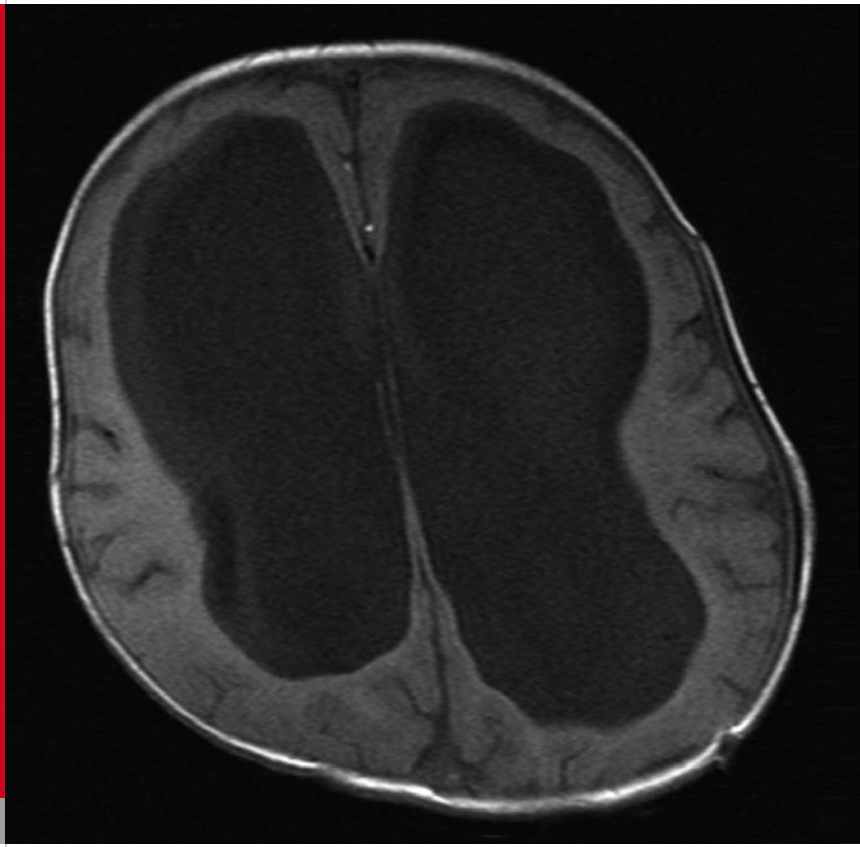

Fig. 2

MRI (T1 sequence, axial view) of the head showing massive hydrocephalus.

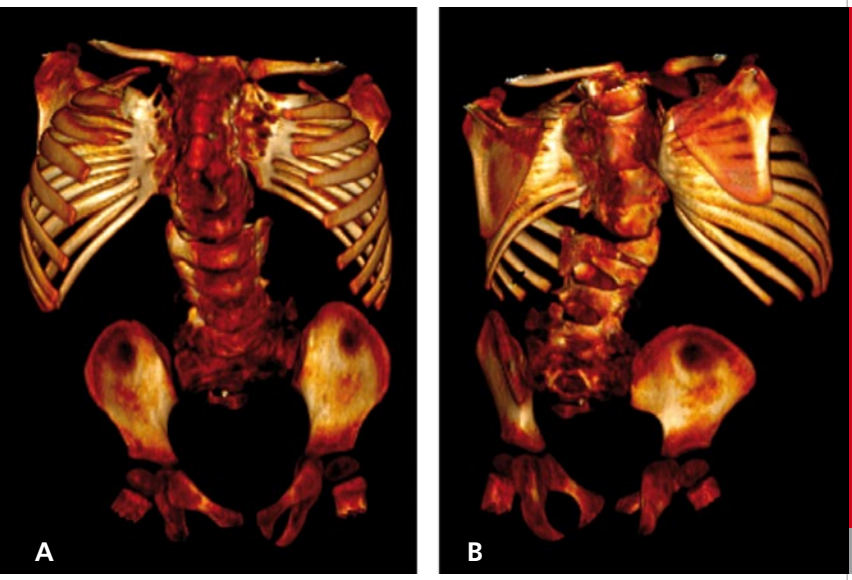

Fig. 3

3D-reconstruction of thoracic CT-scan (A: ap view; B: pa view; see also movie).

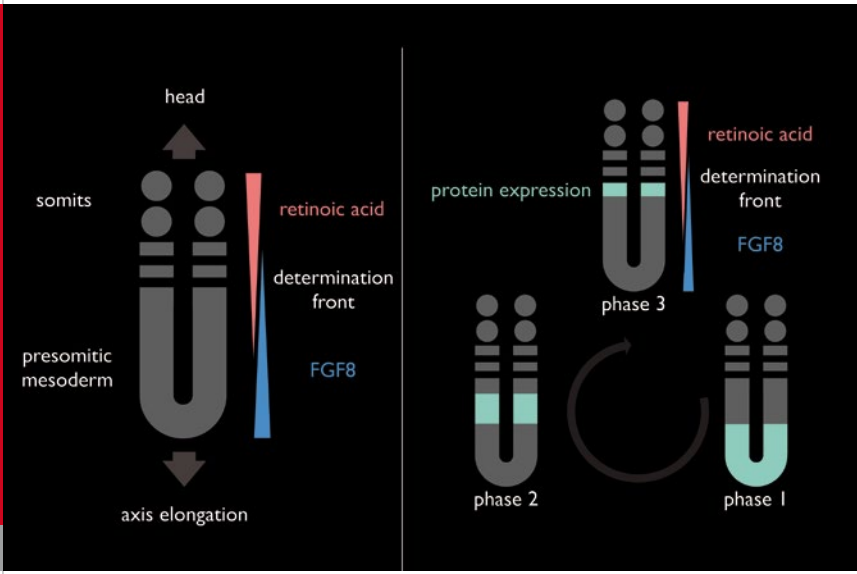

Fig. 4

Somitogenesis: A) The wavefront consists of inverse concentration gradients of FGF8 and retinoic acid. At the determination front, FGF8 levels decrease below a certain value and cells gain the competence to form somites, B) The segmentation clock. Expression of rhythmic gene products (proteins) is initiated in the posterior PSM (phase I). This expression region then moves to the anterior PSM (phase II) and finally stops near the anterior ends (phase III) at the determination front, where somites are formed.

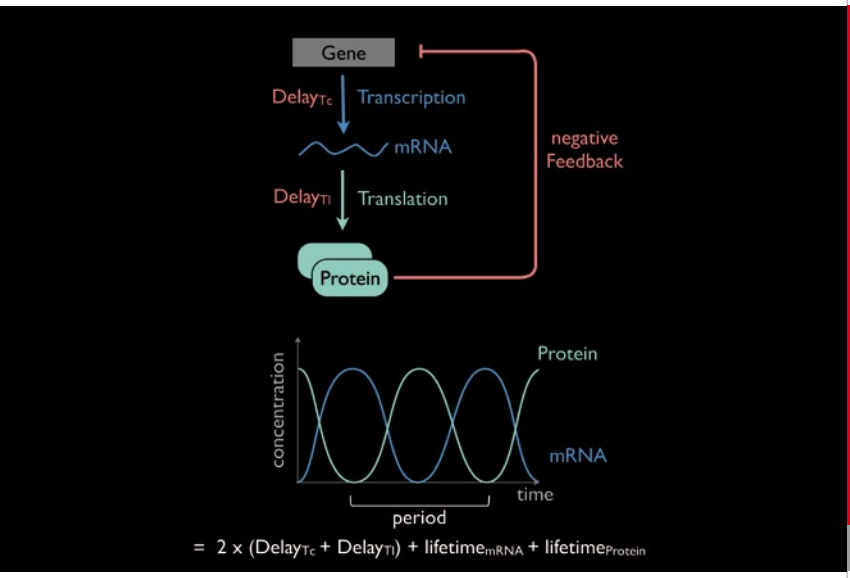

Fig. 5

Oscillating gene expression in the cells of the PSM: The rhythmic gene expression is regulated by negative feedback. Mathematic modeling postulates a transcriptional (Tc) and translational (Tl) delay as well as short lifetimes of the mRNA and the protein of oscillating genes.

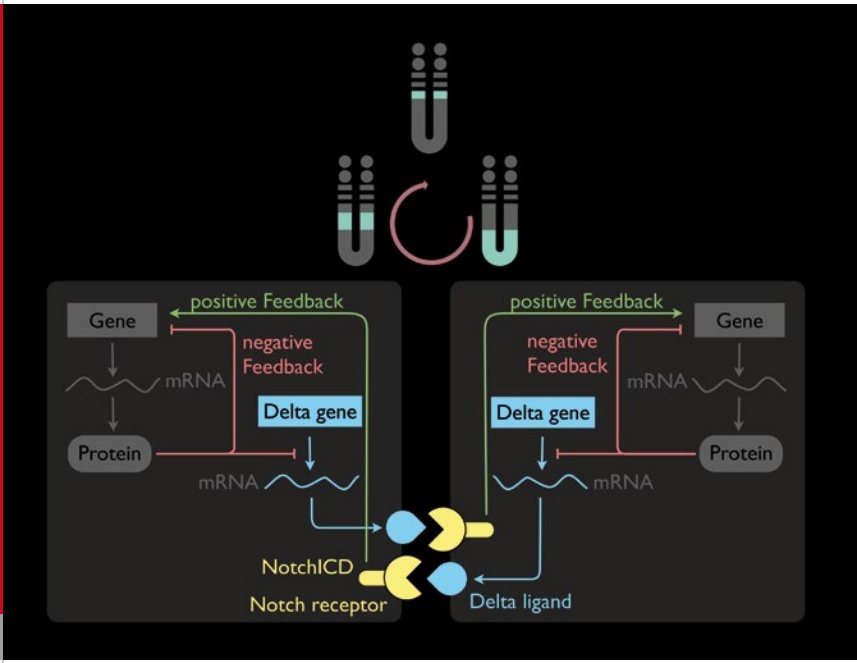

Fig. 6

Synchronization of the oscillations between cells via Notch signaling: A transmembrane protein (Delta) on the surface of one cell binds to a transmembrane receptor (Notch) on the surface of its neighbor. This triggers cleavage of Notch, releasing an intracellular fragment (NotchICD). NotchICD translocates to the cell nucleus and acts there as a transcription regulator, stimulating expression of the clock genes.

In 1938, Jarcho and Levin (1) described two patients with shortening of the trunk, a reduced number of vertebral bodies with segmentation defects and rib malformations. Since then, the eponym Jarcho-Levin syndrome has been used to describe a wide spectrum of skeletal anomalies that includes abnormal vertebral segmentation and rib deformities. In 1978, Solomon et al. (2) divided the syndrome into 2 types: spondylocostal dysostosis (SCD) and spondylothoracic dysplasia (STD). SCD consists of intrinsic asymmetric rib anomalies with consecutive scoliosis. STD is characterized by a fusion of all the ribs at the costovertebral joints bilaterally and vertebral segmentation defects. Radiographically, the thorax in STD has a "crab-like" appearance. The incidence is unknown for STD, but SCD has a reported prevalence of 0.25 per 10'000 births (3).

Developmentally, the vertebral column is derived from mesodermal cells in a process called somitogenesis. Somites are transient embryonic structures and are the precursors of the vertebrae, the intervertebral discs, the rib cage and the striated muscles of the back. They form from the presomitic mesoderm (PSM) at a rhythmic time period that is characteristic of the species (i.e. 4 to 5 hours in humans). Pairs of somites regularly pinch off from the anterior tip of the PSM in an anterior-to-posterior sequence until a defined number which is also characteristic of the species, is reached (4).

How this process is regulated both in time and space at the molecular level has been investigated in the last decade. The most favored idea of how somitogenesis is achieved is the "Clock and Wavefront" model (5).
Along the PSM longitudinal inverse concentration gradients of fibroblast growth factor 8 (FGF8) and retinoic acid exist. This phenomenon is called the wavefront. The wavefront proceeds in the rostral-caudal direction. For a cell at a particular point in the PSM, the competence to segment will only be achieved once the local concentration of FGF8 has decreased below a certain threshold. This point is named determination front. By reaching it, the cell gains the ability to respond to a chemical signal and to produce a somitic factor (Fig. 4A).

While the wavefront controls where somites will form, the segmentation clock determines when they will form. The segmentation clock consists of several genes that are rhythmically expressed: Pulses of gene expression are followed by degradation of transcripts to undetectable levels, with the length of the complete ON/OFF cycle (period) corresponding to the time it takes to form one complete somite. In 1997, the first oscillatory gene c-hairy1 was identified in the PSM of chicks (6). Since then, there has been a growing body of evidence supporting the concept of this segmentation clock and a network of oscillatory genes has been described. Expression of these rhythmic gene products is initiated in the posterior PSM (phase I). This expression region then moves to the anterior PSM (phase II)

and finally stops near the anterior ends (phase III) at the determination front (Fig. 4B).

The interplay between the determination front and the segmentation clock is essential in somitogenesis. The following two conditions have to be met in order for cells to form a somite; the concentration of FGF8 has to fall below a certain level (determination front) and the products of the rhythmically expressed genes have to reach a maximum.

The oscillatory gene expression is regulated by a negative feedback mechanism (Fig. 5). Mathematical modeling of the feedback loop reveals properties that one might not otherwise have guessed. Sustained oscillations may only be generated if certain conditions are met. The delays involved in transcription and translation are particularly crucial. It is defined as the time when a fresh transcript or protein molecule begins to be synthesized to the time when synthesis of that molecule is completed and the functional molecule is delivered to its site of action. Without such delays, the system would not oscillate. If it is to oscillate, the lifetimes of the mRNA and protein molecules must be short compared with the sum of the delays. The predicted period equals twice the sum of the delays plus the lifetimes (7, 8).

The clock itself arises as an autonomous property of PSM cells: Each cell expresses its rhythmical gene pro-

ducts on its own. But in order to form a whole somite, cell-cell communication is essential and the entire cell group has to oscillate in phase. Cell-cell communication via Notch signaling plays a fundamental role in the synchronization of the oscillations between cells (9) (Fig. 6). In zebra fish mutants with failed Notch signal transmission, it was shown that although the individual cells in the PSM continued to oscillate they gradually drifted out of synchrony resulting in incomplete somite formation (10).

Recently, the genetic etiology of SCD in humans has been linked to three mutations in genes that all are important components of the Notch signaling pathway (11). The gene responsible for STD is still unknown, but linkage to the chromosome 2q has been established. The inheritance for SCD is either autosomal dominant or recessive while STD is always autosomal recessively inherited and patients often have a history of Puerto Rican ancestry (3).

Patients with SCD generally have a good prognosis, probably due in part to the asymmetry of the thoracic anomalies resulting in less restrictive pulmonary disease (12). In contrast, the condition of STD has been described throughout the literature as a lethal disorder mostly due to respiratory complications such as pneumonia and pulmonary hypertension. However, Cornier et al. described a cohort of 27 patients with a survival rate of 56 %. In this series, death occurred within

the first 6 months of life due to respiratory failure secondary to pneumonia. The surviving patients had a normal intelligence and reported a good quality of life (13).

While progressive scoliosis - most commonly seen in SCD - may require operative spine fusion, surgical treatment of the thoracic hypoplasia in STD remains more controversial (3). Cornier et al. (13) and Ramirez et al. (14) argue that surgery to expand the thorax is not necessary: survivors who live past infancy seem to cope well even with severe restrictive lung disease. In contrast, Campbell et al. reported favorable results in patients with STD treated by bilateral VEPTR (vertical expandable prosthetic titanium rib) central wedge opening thoracostomies (3).

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