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**Marden-Walker syndrome: case report and review.** D. N. Schweitzer, D. L. Earl, J. M. Graham, Jr., Medical Genetics Birth Defects Center, UCLA School of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA.

Marden-Walker syndrome is a rare autosomal recessive condition characterized by pre- and post-natal growth deficiency, psychomotor retardation, fixed facial expression, blepharophimosis, cleft palate, arachnodactyly, congenital joint contractures, reduced muscular mass, hypotonia and brain abnormalities. As of 1999, at least 30 cases of Marden-Walker have been reported. Consistent clinical findings are shared by these patients but no pathognomonic neuromuscular pathology has been reported. We report a case with Marden-Walker syndrome who demonstrated the clinical findings described above plus a Dandy-Walker malformation and a tethered spinal cord. We compare his clinical and radiographic findings with those of previously reported children with this syndrome and discuss differential diagnosis. It is important to distinguish Marden-Walker syndrome from Van Den Ende-Gupta syndrome which also includes blepharophimosis, arachnodactyly, congenital joint contractures and autosomal recessive mode of inheritance, but lacks mental retardation, serious brain malformations, microcephaly, failure to thrive and severe joint limitation, which are always present in Marden-Walker syndrome.

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**Sudden death in Proteus syndrome.** A.M. Slavotinek<sup>1</sup>, S. Vacha<sup>1</sup>, K. Peters<sup>2</sup> and L.G. Biesecker<sup>1</sup> Genetic Diseases Research Branch, Office of the Clinical Director, NHGRI, NIH, Bethesda, MD.

We report two children with Proteus syndrome (PS) who died suddenly from pulmonary embolism (PE). Clinical criteria for PS diagnosis adheres to published criteria (Biesecker, et al., 1999). Case 1 was a 9yo male whose manifestations included connective tissue nevi, hemimegacephaly, asymmetric progressive overgrowth of numerous tissues, hyperostoses and cutaneous nevi. He was at home and apparently healthy when he emitted a loud gasp and was soon thereafter found unconscious. He could not be revived and was declared dead on arrival at the hospital. Autopsy revealed that the proximate cause of death was a pulmonary embolus associated with a DVT of the lower extremity. Case 2 was a 17yo female whose manifestations were very similar to case 1, but milder in severity. She was undergoing inpatient treatment for sinusitis and/or refractory otitis media when she unexpectedly arrested. She could not be revived. A full autopsy revealed a large pulmonary embolus with no identified DVT. To our knowledge, PE has previously been reported only in one case of PS. That report described a 2yo male undergoing surgical convalescence who had asymmetric overgrowth, macrodactyly and widespread internal hemolymphangiomas (Eberhard et al., 1994). Although PE may be uncommon in PS, it has been described in Klippel-Trenaunay syndrome (KTS). Venous malformations are a feature of KTS and the incidences of venous thromboembolism and PE have been estimated to be as high as 22% and 12% respectively in KTS (Baskerville et al., 1985). We conclude that PE is a serious complication of PS. We recommend vigilance concerning the signs and symptoms of thrombosis and PE in individuals with PS, including children. Aggressive evaluation and treatment should be considered urgently in patients with PS and signs or symptoms of DVT. This finding may contribute to the apparent increase in mortality in children with PS.

## References

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**Natural history of the Adams-Oliver Syndrome: A report of progressive Central and Peripheral nervous system involvement in a mother and son.**

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The association of aplasia cutis congenita of the scalp with terminal transverse defects of the limbs has been described in 1945 by Adams and Oliver. This predominately autosomal dominant syndrome displays a wide phenotypic variation. Limb and cranial malformations may be associated with cutis mamorata and tortuous dilated scalp veins. Up to 20% of these patients have associated cardiovascular malformations. A variety of brain and cranial malformations have been reported in AOS and dysplasia of the cerebral cortex has been only recently reported in one case. We report on a 27 year old man who was diagnosed by us (NS) at the age of 3 years with typical findings of AOS. At that time, his mother was found to have only subtle distal phalangeal hypoplasia. A maternal aunt and her daughter were more typically affected. Our patient was a physically active young child. Cognitive evaluation at school age revealed borderline to mild mental retardation. He attended school through his late teens and worked until the age of 24 years. He then experienced progressive asymmetrical spastic weakness making him wheelchair dependent and developed dysphasia to the point that his speech became unintelligible. At his most recent admission to the hospital he exhibited severe spasticity in the legs and weakness in the arms involving the left side more than the right side. Vocal cord motion was normal, but swallowing was poorly coordinated with weak lingual, buccal and pharyngeal motion. Brain MRI showed pronounced asymmetrical cerebral atrophy and asymmetrical cerebral hypoplasia. His mother's recent examination revealed dysarthria, weakness with wheelchair dependence and mild spasticity, which she experienced over a 10 year interval. Her brain MRI revealed very similar findings to those described in her son. Additional results of studies done on both patients will be presented as well as a review of the literature.

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**Severe Saethre-Chotzen syndrome in an infant with a complex chromosome rearrangement.** A.L. Storm<sup>1</sup>, T.C. Drumheller<sup>1</sup>, S.N. Katz<sup>1</sup>, J. Low<sup>1</sup>, C. Airheart<sup>1</sup>, K.W. Gripp<sup>2</sup> and C. Curry<sup>1</sup>. <sup>1</sup>Valley Children's Hospital/UCSF, Madera, CA and <sup>2</sup>Children's Hospital of Philadelphia, PA.

Saethre-Chotzen syndrome (SCS) is an autosomal dominant craniosynostosis syndrome with variable expression. Analysis of chromosome translocations found in patients with SCS played an important role in mapping the SCS gene to 7p21 and the subsequent identification of the TWIST gene. SCS has been associated with point mutations within the TWIST gene as well as deletion of the entire gene. The purpose of this report is to present a patient with severe craniofacial features of SCS who has a complex chromosome anomaly.

The patient was a product of a term gestation complicated by fetal ventriculomegaly and oligohydramnios. Physical examination in the neonatal period revealed cranial and facial asymmetry, brachycephaly, low posterior and anterior hairlines, midface hypoplasia, ptosis, broad thumbs and toes, and cryptorchidism. Imaging demonstrated bilateral coronal suture fusion, dilated lateral ventricles, partial agenesis of the corpus callosum, and a large cisterna magna. An echocardiogram revealed a VSD and ASD. At two months of age the infant had a bifrontal craniotomy and bilateral orbito-zygomatico-temporal osteotomies. At three months of age he appears to be developmentally delayed.

The infant has a balanced four-way translocation between 1q, 2q, 7p, and 18p and a separate translocation between 7q and 18q. Parental karyotypes are normal. Successive FISH analyses using dual color whole chromosome paints, centromeric alpha satellite probes, and a telomeric probe for 18p confirmed these findings. The breakpoint on the short arm of chromosome 7p is assigned to 7p15.3 and does not appear to interrupt band 7p21. Sequencing of the TWIST gene and FISH analysis using a probe specific for the TWIST region were normal. Southern blot analysis to assess dosage of the TWIST gene is pending. Mutation analysis of the FGFR genes and comparative genomic hybridization are planned.

It is possible that this infant's phenotype is the result of position effect on the TWIST gene or disruption of other genes associated with craniosynostosis. This expanded cytogenetic and molecular armamentarium may allow us to determine the pathogenesis of this infant's condition and may provide further insight into the mechanisms for SCS.