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Case report

Salicylate-induced consumption coagulopathy

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Raised serum transaminase levels in juvenile rheumatoid arthritis (JRA) treated with salicylates have been reported by Russell, Sturge, and Smith (1971). The present communication describes a second complication apparently coinciding with this sign of liver injury during administration of salicylates.

Methods

Serum transaminases were determined according to the method of Karmen, Wrobleski, and La Due (1955) (normal values for our laboratory: SGOT and SGPT up to 15 i.u./litre), serum salicylate levels with Trinder's reagent, fibrinogen according to the method of Clauss (1957), fibrinogen degradation products (FDP) by the immunodiffusion technique (Ouchterlony), and Factor V according to the method of Borchgrevink, Pool, and Stormorken (1960).

Case report

A 15-year-old boy was referred to the Leiden University Medical Centre. During hospitalization elsewhere he had been treated for suspected rheumatic fever with salicylates in doses up to 6 g. daily for 2 weeks, and 3 days before his admission at Leiden, the excision of a lymph node from the right axilla (histology: non-specific inflammation) had resulted in profuse bleeding requiring five blood transfusions (2,500 ml.). Thrombocytopenia had been demonstrated (thrombocytes 20,000 per μl.). Salicylates had been discontinued 2 days before admission and replaced by high doses of corticosteroids. In spite of this treatment the patient's general condition deteriorated.

Examination
He was a pale sick boy, slightly jaundiced, with enlarged non-tender lymph nodes in the neck and left axilla, hepatosplenomegaly, and a (transient) macular rash over the trunk. Body temperature 36·7°C., pulse rate 35 (a transient, unexplained sinus bradycardia), respiration rate 16, blood pressure 120/80 mm. Hg, and body weight 41·2 kg. In the right axilla there was a surgical wound which bled slightly. Fundoscopy revealed a small right-sided retina haemorrhage.

There was no overt swelling of the joints.

Laboratory investigations
Erythrocyte sedimentation rate 3 mm./1st hr; haemoglobin 15 g./100 ml.; reticulocytes 50 per cent.; leucocytes 9,000/μl.

Blood smear: anisocytosis, poikilocytosis, and polychromasia of the red cells, some normoblasts, no fragmentation; leucocytes: moderate shift to the left and toxic granulation; thrombocytes 35,000/μl. Bleeding time 10 min. 40 sec.; prothrombin time 20 sec. (control 13·5 sec.); Factor V 56 per cent.; fibrinogen 45 mg per cent. FDP positive. SGOT 232 i.u./litre, SGPT 160 i.u./litre, SLDH 520 i.u./litre (normal values up to 160 i.u./litre). Bilirubin direct 4·15 mg. per cent, total 5·95 mg. per cent, alkaline phosphatase 83·7 K.A. units. Serum protein 62·9 g./litre, serum albumin 29·9 g./litre.

Treatment
Corticosteroids were discontinued.

Course
In the first week the serum transaminase and bilirubin values became normal, the erythrocyte sedimentation rate rose to 47 mm./1st hr, thrombocytes to 150,000/μl., and fibrinogen to 180 mg. per cent. FDP disappeared (Figure).

During the following week a high spiking fever and the rash recurred. Arthritis of the left hip and knee and finally a widespread chronic polyarthritis developed. These manifestations, together with a transient lymphadenopathy, splenomegaly, and leucocytosis (up to 15,600/μl.), were highly suggestive of Still's disease (JRA). Infectious diseases and malignancies could be excluded.

Because of the diagnosis of JRA, salicylates were administered in a dosage of 4 g./day. On this regime the classical signs of salicylism appeared: the liver function again deteriorated, the serum transaminase levels rose, and consumption coagulopathy developed (Figure).

Upon discontinuation of salicylates after 4 days of treatment, the transaminase levels returned to normal within a week and the coagulopathy disappeared. Thereafter salicylates were given for the third time, but in a gradually increasing dosage starting with 2 g./day. At a point between 3 and 4 g. /day, elevation of transaminase

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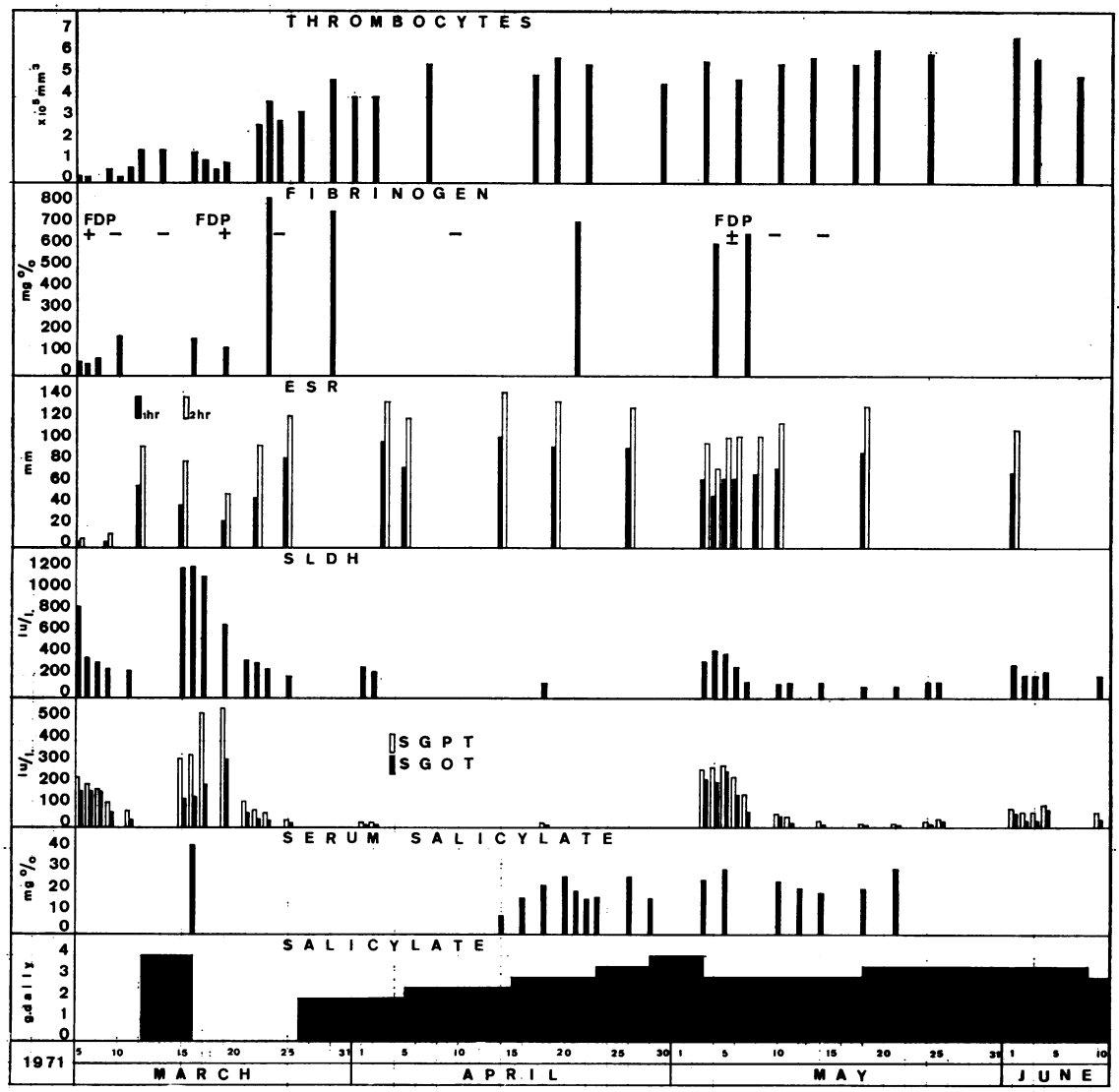

FIGURE. *Effect of salicylate dosage on serum-salicylate level, SGOT, SGPT, SLDH, fibrinogen, and thrombocyte count in a patient with juvenile rheumatoid arthritis*

levels recurred although not to the same degree as before. There was a moderate drop in the erythrocyte sedimentation rate but the FDP test was inconclusive. At that time the serum albumin had reached an almost normal value.

Results

At present, one year after admission, the initial diagnosis of JRA has been confirmed, the only clinical sign being a gradually improving arthritis of the knees and wrists. On sustained well-controlled salicylate therapy (3 g./day), the general condition of the patient and the arthritis have improved. An attempt to provoke consumption coagulopathy with a higher dose of salicylate (4 g./day) failed.

Discussion

This 15-year-old boy with JRA repeatedly showed a significant increase in serum transaminase when given salicylates. This almost certainly reflected liver cell injury. Twice the highest levels of serum transaminase were accompanied by consumption coagulopathy, once resulting in severe postoperative bleeding. It is impossible for liver parenchymal cell dysfunction alone to have caused such a severe hypofibrinogenaemia (45 mg. per cent.), since the prothrombin time was only moderately prolonged. It could be that the salicylate therapy itself contributed to the thrombocytopenia, but since we found abnormal amounts of

FDP in the patient's serum we assume that intravascular coagulation, possibly only in the liver, caused the hypofibrinogenaemia and thrombocytopenia. On a third occasion, when there was only a slight rise in the serum transaminase levels, tests for consumption coagulopathy were inconclusive. The failure to induce consumption coagulopathy 6 months after admission may be related to the clinical and biochemical improvement. Serum albumin, which binds about 70 per cent. of the salicylate, had increased from 20 to 39 g./litre.

Elevation of serum transaminase levels after salicylate administration has been observed in animals (Janota, Wincey, Sandiford, and Smith, 1960), children with rheumatic fever (Manso, Taranta, and Nydick, 1965), and recently in children with JRA (Russell and others, 1971). The latter ruled out the possibility that salicylates interfere with the serum transaminase assay at the salicylate levels under discussion.

The rise in serum transaminase levels in our patient, among others, was accompanied by a deterioration of liver function. This, and the fact that the histological picture of the liver in salicylate-treated animals is characterized by cloudy swelling and fatty infiltration (Janota and others, 1960), makes liver injury the most likely explanation for the increased serum transaminases. A liver biopsy was not performed on our patient because of the haemorrhagic diathesis caused by the consumption coagulopathy.

Study of the literature has failed to yield any report of a relationship between consumption coagulopathy and salicylate dosages, as suggested here. However, Kornreich, Malouf, and Hanson (1971) described seven children with acute changes in hepatic function during the course of JRA. Five of these patients, who were treated with salicylates, showed an abrupt drop in the Erythrocyte Sedimentation rate concomitant with the appearance of hepatic dysfunction as well as raised serum transaminase levels. The fact that these patients also had consumptive coagulopathy is highly suggestive.

At this stage it would, however, be premature to discuss a possible causal relationship between liver injury and consumption coagulopathy, although other coincidences have been observed, particularly in cases of acute fatty metamorphosis of the liver occurring in the last weeks of pregnancy (Sheehan, 1961; Gevers, Loeliger, Veltkamp, Kreuning, and de Jong, 1969), acute hepatic necrosis (Rake, Flute, Pannell and Williams, 1970), and liver cirrhosis (Johansson, 1964).

It is well known that salicylates induce thrombocytopathy. Our case demonstrates that consumption coagulopathy may occur as well. This stresses the need for extreme precaution when biopsies or other surgical procedures are considered for patients being treated with salicylates.

Summary

Consumption coagulopathy related to salicylate therapy is described in a patient suffering from juvenile rheumatoid arthritis. This hitherto unreported complication coincided with signs of liver injury described by other workers.

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References

BORCHGREVINK, C. F., POOL, J. G., AND STORMORKEN, H. (1960) *J. Lab. clin. Med.*, **55**, 625 (A new assay for factor V (pro-accelerin-accelerin) using Russell's viper venom)

CLAUSS, A. (1967) *Acta haemat. (Basel)*, **17**, 237 (Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens)

GEVERS, R. H., LOELIGER, E. A., VELTKAMP, J. J., KREUNING, J., AND DE JONG, U. W. (1969) *Ned. T. Geneesk.*, **113**, 1526. (Acute leververvetting in de zwangershap)

JOHANSSON, S. A. (1964) *Acta med. scand.*, **175**, 177 (Studied on blood coagulation factors in a case of liver cirrhosis. Remission of the hemorrhagic tendency on treatment with heparin)

JANOTA, I., WINCEY, C. W., SANDIFORD, M., AND SMITH, M. J. H. (1960) *Nature (Lond.)*, **185**, 935 (Effect of salicylate on the activity of plasma enzymes in the rabbit)

KARMEN, A., WRÓBLEWSKI, F., and LA DUE, J. S. (1955) *J. clin. Invest.*, **34**, 126 (Transaminase activity in human blood)

KORNREICH, H., MALOUF, N. N., AND HANSON, V. (1971) *J. Pediat.*, **79**, 27 (Acute hepatic dysfunction in juvenile rheumatoid arthritis)

MANSO, C., TARANTA, A., AND NYDICK, J. (1956) *Proc. Soc. exp. Biol. (N.Y.)*, **93**, 84 (Effect of aspirin administration on serum glutamic oxaloacetic and glutamic pyruvic transaminases in children)

RAKE, M. O., FLUTE, P. T., PANNELL, G., AND WILLIAMS, R. (1970) *Lancet*, **1**, 533 (Intravascular coagulation in acute hepatic necrosis)

RUSSELL, A. S., STURGE, R. A., SMITH, M. A. (1971) *Brit. med. J.* **2**, 428 (Serum transaminases during salicylate therapy)

SHEEHAN, H. L. (1961) *Amer. J. Obstet. Gynec.*, **81**, 427 (Jaundice in pregnancy)